L32 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2003 ACS
AN 2002:384291 CAPLUS
DN 136:374566
TI Skin composition containing 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components
IN Koga, Nobuyoshi; Maruyama, Nao; Sakamoto, Tetsuo; Tomita, Kenichi
PA Shiseido Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 30 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K007-48
ICS A61K007-00; A61K031-17; A61K031-195; A61K031-203; A61K031-351; A61K031-355; A61K031-375; A61K031-4164; A61K031-4415; A61K031-565; A61K031-7032; A61K031-7048; A61K031-728; A61K035-78; A61P017-16; A61P043-00
CC 62-4 (Essential Oils and Cosmetics)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 2002145759	A2	20020522	JP 2001-246127	20010814
PRAI JP 2000-257283	A	20000828		

OS MARPAT 136:374566
AB The invention relates to a skin compn. providing improved skin-lightening effect, wherein the compn. contains 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active component, e.g. vitamin A acid, vitamin B6 hydrochloride, Lamium album ext., allantoin, DL-.alpha.-tocopherol-2-L-**ascorbic** acid **phosphate** diester, vitamin E, **hydroquinone** glycoside, saikosaponin, tranexamic acid, kojic acid, rutin, placenta ext., ethynylestradiol, urocanic acid, mucopolysaccharide, and/or their deriv. A cosmetic emulsion contg. polyoxyethylene polyoxypropylene cetyl alc. ether 1, silicone KF 96 2, liq. paraffin 3, propylene glycol 5, glycerin 2, Et alc. 5, carboxyvinyl polymer 0.3, hydroxypropyl cellulose 0.1, 2-aminomethyl propanol 0.1, vitamin A acid 0.05, 2-O-.alpha.-glucopyranosyl-L-ascorbic acid 2, preservative and fragrance q.s., and water balance to 100 % was prepd.
ST glycopyranosyl ascorbate skin lightening cosmetic
IT Surfactants
(amphoteric; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)
IT Surfactants
(anionic; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)
IT Cosmetics
(creams; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)
IT Cosmetics
(emulsions; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)
IT Lamium album
(exts.; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)
IT **Hydroquinones**
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(glycoside; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)
IT Castor oil
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(hydrogenated, ethoxylated; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)
IT Cosmetics

(lotions; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)

IT Cosmetics
(packs; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)

IT Cosmetics
(powders; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)

IT Surfactants
(semipolar; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)

IT Amine oxides
Betaines
Mucopolysaccharides, biological studies
Placental hormones
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)

IT Cosmetics
(skin-lightening; skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)

IT 57-63-6, Ethynylestradiol 58-95-7, Tocopherol acetate 97-59-6, Allantoin 102-71-6, Triethanolamine, biological studies 104-98-3, Urocanic acid 151-21-3, Sodium lauryl sulfate, biological studies 153-18-4, Rutin 302-79-4, Vitamin A acid 497-76-7, Arbutin 501-30-4, Kojic acid 683-10-3, Lauryldimethylaminoacetate betaine 1197-18-8, Tranexamic acid 1323-39-3, Propylene glycol stearate 1406-18-4, Vitamin E 2571-88-2, Dimethylstearyl amineoxide 7360-38-5, Glyceryl tri-2-ethylhexanoate 9004-61-9, Hyaluronic acid 9004-95-9, Polyoxyethylene cetyl ether 9004-96-0, Polyoxyethylene monooleate 9004-98-2, Polyoxyethylene oleyl alcohol ether 9005-67-8, Polyoxyethylene sorbitan monostearate 12001-77-3, Vitamin B6 hydrochloride 25496-72-4, Glycerin monooleate 31566-31-1, Glyceryl monostearate 37311-01-6, Ethylene oxide-propylene oxide copolymer cetyl ether 58316-41-9, Saikosaponin b2 63705-03-3, Polyglyceryl diisostearate 67938-21-0, Diglyceryl diisostearate 84101-04-2, Polyoxyethyleneglyceryl monoisostearate 96301-17-6 98253-20-4, Saikosaponin 102033-55-6, Decaglycerin diisostearate 129499-78-1 130603-71-3 132697-38-2
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(skin-lightening compn. contg. 2-O-glucopyranosyl-L-ascorbic acid in **combination** with other active components)

L32 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2003 ACS
AN 2000:383138 CAPLUS
DN 134:61209
TI An innovative cosmeceutical with skin-whitening activity. Note 1.
AU Morganti, P.; Fabrizi, G.; James, B.
CS President/Director, R. and D - Mavi Sud S.r.l., Aprilia, 04011, Italy
SO Journal of Applied Cosmetology (1999), 17(4), 144-153
CODEN: JACOEL; ISSN: 0392-8543
PB International Ediemme
DT Journal
LA English
CC 62-4 (Essential Oils and Cosmetics)
Section cross-reference(s): 63
AB Hyperpigmentation is a skin disturbance affecting many people all over the world. Among the different bleaching cosmetic products, the most commonly used active ingredients are **hydroquinone**, azelaic acid, kojic acid, ellagic acid, rucinol, arbutin and different vitamin C derivs. In fact, vitamin C is widely known to have a suppressing effect on melanic pigmentation, but because of its easy decompn., a variety of stabilized vitamin C derivs. have been developed and commercialized. The main problem of these derivs. is their difficulty to target the stratum corneum

(SC) for acting specifically on functioning melanocytes with active synthesis of melanin. The aim of this study was to control the **combined** activity of arbutin ext., hexadecanoyl ascorbic acid (VC-IP) and magnesium L-**ascorbyl**-2-**phosphate** (VC-PMG), to suppress melanic pigmentation (product A). At the same time, we wanted to control the depigmenting activity and the product stability of the ascorbic-acid, included in a kojic-based cosmetic formulation utilizing a new 2-chamber dispenser (SYMBIO), which allows to keep vitamin C sep. from the other ingredients (product B). Skin absorption-potential through the skin of the cosmetic vehicles and active ingredients were controlled by the dansyl chloride methodol., stripping the SC at different levels. Clin. evaluation of the obtained lightening effect was performed on 40 randomized female volunteers over a period of 3 mo by the clin. score and the Minolta Chromameter CR 200 methods. The topical application of both the products (A and B) was effective in lightening the skin of the majority of the treated patients, showing a remarkable penetrability degree and a mean redn. of the skin hyperpigmentation from 30 to 45%. L-ascorbic acid-based formulation was superior of about 20% to VC-PMG-based in restoring to normal the hyperpigmentation skin disorders, such as senile freckles. Both the formulations were well tolerated during the study term.

ST ascorbate cosmeceutical skin lightening; palmitate ascorbate cosmeceutical skin

IT Skin, disease
(hyperpigmentation; cosmeceutical with skin lightening activity)

IT Cosmetics
(skin-lightening; cosmeceutical with skin lightening activity)

IT Skin
(stratum corneum; cosmeceutical with skin lightening activity)

IT Drug delivery systems
(topical; cosmeceutical with skin lightening activity)

IT 50-81-7, L-Ascorbic acid, biological studies 137-66-6, Ascorbyl palmitate 23666-04-8, Magnesium **ascorbyl**-2-**phosphate**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cosmeceutical with skin lightening activity)

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD

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(19) Tachibana, S; Fragrance J 1997, V1997-9, P37

L32 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2003 ACS
AN 1999:225625 CAPLUS
DN 130:271884
TI Skin-lightening preparations containing glutathione

IN Yagi, Eiichiro; Naganuma, Masako
PA Shiseido Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K007-00
ICS A61K007-00; A61K007-48; A61K031-19; A61K031-34; A61K031-35; A61K031-375; A61K031-70; A61K035-50
CC 62-4 (Essential Oils and Cosmetics)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 11092326	A2	19990406	JP 1997-275262	19970922
PRAI	JP 1997-275262		19970922		

AB Skin-lightening prepns. contain glutathione and L-ascorbic acid (derivs.), placenta exts., kojic acid (derivs.), azelaic acid (derivs.), glucosamine (derivs.), **hydroquinone** glycosides (derivs.), tranexamic acid (derivs.), and/or ellagic acid (derivs.). The prepns. show excellent skin-lightening effects.
ST glutathione ascorbate placenta kojate skin lightening; azelate glucosamine tranexamate glutathione skin lightening; **hydroquinone** glycoside ellagate glutathione skin lightening
IT Placenta
(exts.; cosmetics contg. glutathione **combined** with other skin-lightening agents)
IT Glycosides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**hydroquinone**; cosmetics contg. glutathione **combined** with other skin-lightening agents)
IT Cosmetics
(skin-lightening; cosmetics contg. glutathione **combined** with other skin-lightening agents)
IT 50-81-7, L-Ascorbic acid, biological studies 70-18-8, Glutathione, biological studies 123-31-9D, **Hydroquinone**, glycosides 123-99-9, Azelaic acid, biological studies 476-66-4, Ellagic acid 497-76-7, Arbutin 501-30-4, Kojic acid 1197-18-8, Tranexamic acid 3416-24-8, Glucosamine 37627-95-5, L-Ascorbic acid 2-sulfate 66651-98-7, L-**Ascorbic** acid 2-sulfate sodium **salt** 74438-74-7, Ascorbic acid distearate 108910-78-7, L-**Ascorbic** acid **phosphate** magnesium **salt** 125913-31-7, L-**Ascorbic** acid **phosphate** 129499-78-1, L-Ascorbic acid 2-glucoside
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(cosmetics contg. glutathione **combined** with other skin-lightening agents)

L32 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2003 ACS
AN 1997:618653 CAPLUS
DN 127:322665
TI Skin-lightening topical preparations containing escinol
IN Maeda, Norihisa; Naganuma, Masako
PA Shiseido Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K007-00
ICS A61K007-00; A61K007-48; A61K035-78; C07J063-00
CC 62-4 (Essential Oils and Cosmetics)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 09241124	A2	19970916	JP 1996-78364	19960306
PRAI	JP 1996-78364		19960306		

OS MARPAT 127:322665

AB Title topical prepns. contain L-ascorbic acids, placenta exts., kojic acids, azelaic acids, glucosamines, **hydroquinone** glycosides, and/or licorice exts. and escinol (triterpenoid saponin glycosides) or its salts. A topical prepn. contg. 0.2 % escinol and 2.0 % **ascorbic** acid **phosphate** Mg **salt** showed good skin-lightening effect in humans.

ST ascorbate placenta ext escinol skin lightening; kojic azelaic acid escinol skin lightening; glucosamine **hydroquinone** glycoside escinol skin lightening; licorice ext escinol skin lightening

IT Licorice (Glycyrrhiza)
Placenta
(exts.; topical prepns. contg. escinol **combined** with other skin-lightening agents)

IT Glycosides
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**hydroquinone**; topical prepns. contg. escinol **combined** with other skin-lightening agents)

IT Cosmetics
(skin-lightening; topical prepns. contg. escinol **combined** with other skin-lightening agents)

IT Saponins
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(triterpenoid; topical prepns. contg. escinol **combined** with other skin-lightening agents)

IT 50-81-7, L-Ascorbic acid, biological studies 123-99-9, Azelaic acid, biological studies 497-76-7 501-30-4, Kojic acid 3416-24-8, Glucosamine 28474-90-0, L-Ascorbic acid dipalmitate 37627-95-5, L-Ascorbic acid 2-sulfate 74438-74-7, L-Ascorbic acid distearate 92353-27-0, L-Ascorbic acid dioleate 108910-78-7, L-**Ascorbic** acid **phosphate** magnesium **salt** 125913-31-7, L-**Ascorbic** acid **phosphate** 127120-27-8, Escinol 128808-26-4, L-**Ascorbic** acid **phosphate** sodium **salt**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(topical prepns. contg. escinol **combined** with other skin-lightening agents)

L32 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2003 ACS

AN 1960:94633 CAPLUS

DN 54:94633

OREF 54:17918c-e

TI Comparison of some synergistic antioxidants in a methyl linoleate-water system

AU Spetsig, Lars Olov

SO Arkiv Kemi (1959), 15, 23-30

DT Journal

LA English

CC 27 (Fats, Fatty Oils, Waxes, and Detergents)

AB In **combination** with **hydroquinone** at pH 4.0 ascorbyl palmitate (I) showed some beneficial effect, but ascorbic acid (II), thioglycolic acid (III), and Na bisulfite (IV) were detrimental. With diphenyl-p-phenylenediamine as a primary autoxidant I and II had a protective effect, but III and IV were detrimental. Glycine and alanine had adverse effects on **hydroquinone** (V), butylated hydroxyanisole (VI), and nordihydroguaiaretic acid (VII). Phosphoric,

maleic, malonic, citric, tartaric, and malic acids had small pos. or neg. effects on V, VI, and VII, but had strong synergistic effects on phenyl-1-naphthylamine and diphenyl-p-phenylenediamine in slightly acidic soln., as had also malonic acid, ascorbic acid, and ascorbyl palmitate. On V, VI, and VII thioglycolic acid and Na bisulfite were detrimental in alk. soln. Only glycine and citric acid showed any influence on diarylamine antioxidants.

IT Amines
(antioxidants of diaryl, in Me linoleate-H2O system, citric acid and glycine as synergists with)

IT Phenols
(antioxidants, in Me linoleate-H2O system, synergistic antioxidants for)

IT Antioxidants
(diarylamine and phenolic, in Me linoleate-H2O system, synergistic)

IT Tartaric acid
(as antioxidant (synergistic) with arylamines in aq. Me linoleate)

IT Palmitic acid, **ester** with **ascorbic** acid
(as antioxidant synergist with amines and phenols in Me linoleate-H2O system)

IT 77-92-9, Citric acid
(antioxidant mixts. with arylamines, in aq. Me linoleate)

IT 7664-38-2, Phosphoric acid
(antioxidants from arylamine antioxidants in Me linoleate-H2O system and)

IT 141-82-2, Malonic acid
(antioxidants from arylamines and, in aq. Me linoleate)

IT 6915-15-7, Malic acid
(antioxidants from arylamines, aq. Me linoleate and)

IT 56-40-6, Glycine
(antioxidants from diarylamines and, in aq. Me linoleate)

IT 110-16-7, Maleic acid
(as antioxidant (synergistic) with arylamines in aq. Me linoleate)

IT 90-30-2, 1-Naphthylamine, N-phenyl-
(as antioxidant for 3-carene, in Me linoleate-H2O system and synergism of acids therewith)

IT 29728-85-6, p-Phenylenediamine, diphenyl-
(as antioxidant in Me linoleate-H2O system and synergistic effects with acids)

IT 137-66-6, Ascorbic acid, palmitate
(as antioxidants synergistic with amines and phenols in Me linoleate-water system)

IT 112-63-0, Linoleic acid, methyl ester
(synergistic antioxidants for diarylamines and polyphenols in aq.)

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SUMM Preferably, the iminium ion scavenger is used in **combination** with a nitrite ion scavenger. The term "nitrite ion scavenger" as used herein denotes an agent which reacts with the nitrite ion more readily than does a nitrosatable amine such as morpholine. Suitably, the nitrite ion scavenger is chosen such that at a concentration of 1M, preferably 500 mM, preferably 100 mM, suitably 10 mM, it reduces the rate of formation of nitrosamines by at least about 25%, preferably at least about 50%, preferably at least about 75%, preferably at least about 90%, especially at least about 95% in a model system comprising 44 mM morpholine and 0.8 mM nitrite ions at pH 5 and 25.degree. C. Typically, nitrite ion scavengers are antioxidants such as **ascorbate**, isoascorbate, **ascorbyl** peptides, **ascorbyl** **phosphates**, (such as magnesium **ascorbyl** **phosphate** from Nikko Chemicals, Japan), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), .alpha.-tocopherol, **hydroquinone** or catechol. As noted above, however, they may also be amines such as urea and hydrazide or amides such as methylsulphonamide or other compounds such as phenols, anilines and alkenes. The azide ion is also a nitrite ion scavenger, as it reacts with nitrite to form unstable nitrosyl azide which then decomposes to form nitrogen and nitrous oxide.

of a composition, although amounts outside this range can be used. Antioxidants include, but are not limited to, one or more of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tertiary butyl **hydroquinone** (TBHQ), ethoxyquin and salts thereof, dilauryl thiodipropionate (DLTDP), n-propyl gallate, tocopherols, tocotrienols, **hydroquinone** and esters thereof, gallic acid **salts** and **esters** thereof, gamma oryzanol, **ascorbic** acid and ascorbates, ascorbyl palmitate and dipalmitate, like substances, and **combinations** thereof.

SUMM The advantage to forming pellets of the container material is the low degree of toxicity and ease of handling. The pellets encapsulate any toxic substances in a homogenized solid or pelletized form. Therefore, if this material is accidentally ingested, it will pass through a body without being absorbed. Further, the pellets are unlikely to create or cause dust, which might cause irritation if it comes into contact with the **skin**, eyes or mucus membranes.

PI US 6057015 20000502

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DETD [0017] Fat-soluble fatty acid **esters** of **ascorbic** acid (vitamin C) are employed as alternate or additional adjunct ingredients in other embodiments, alone or in **combination** with **hydroquinone** or .alpha.-hydroxy acids. The more oxidation-resistant saturated fatty acid **esters** of **ascorbic** acid are preferred, including, but not limited to, ascorbyl laurate, ascorbyl myristate, ascorbyl palmitate, ascorbyl stearate, and ascorbyl behenate. Ascorbyl palmitate is used in one embodiment. As denoted herein, where fatty acid esters are described, e.g., ascorbyl stearate, compositions having predominantly that ester, e.g., predominantly stearate, are included. The esters may be prepared using hydrogenated oils or fats, or fractions thereof, and contain small amounts of another ester. Ascorbyl stearate prepared using canola, for example, commonly contain about 4% ascorbyl palmitate. It is an advantage of the invention that where fatty acid esters of ascorbic acid are employed as an adjunct ingredient, they help provide emollient properties to the composition. Typical concentration ranges of ascorbyl palmitate vary from about 0.25% to about 10%, more narrowly from about 2% to about 8%, and even more narrowly from about 3% to about 5% by weight.

DETD [0018] However, only effective amounts of active ingredient(s) are needed to whiten **skin**, so generally topical application to **skin** sites is accomplished in association with a carrier, and particularly one in which the active ingredient is soluble per se or is effectively solubilized (e.g., as an emulsion or microemulsion). Where employed, the carrier is inert in the sense of not bringing about a deactivation or oxidation of active or adjunct ingredient(s), and in the sense of not bringing about any adverse effect on the **skin** areas to which it is applied. In one preferred practice of the invention, hydroxytetronic acids are applied in admixture with a dermatologically acceptable carrier or vehicle (e.g., as a lotion, cream, ointment, soap, stick, or the like) so as to facilitate topical application and, in some cases, provide additional beneficial effects as might be brought about, e.g., by moisturizing of the affected **skin** or mucosal areas. While the carrier for dermatological compositions can consist of a relatively simple solvent or dispersant such as water, it is generally preferred that the carrier comprise a composition more conducive to topical application, and particularly one which will form a film or layer on the **skin** to which it is applied so as to localize the application and provide some resistance to washing off by immersion in water or by perspiration and/or aid in the percutaneous delivery of the active agent. Many preparations are known in the art, and include lotions containing oils and/or alcohols and emollients such as olive oil, hydrocarbon oils and waxes, silicone oils, other vegetable, animal or marine fats or oils, glyceride derivatives, fatty acids or fatty acid esters or alcohols or alcohol ethers, lecithin, lanolin and derivatives, polyhydric alcohols or esters, wax esters, sterols, phospholipids and the like, and generally also emulsifiers (nonionic, cationic or anionic), although some of the emollients inherently possess emulsifying properties. These same general ingredients can be formulated into a cream rather than a lotion, or into gels, or into solid sticks by utilization of different proportions of the ingredients and/or by inclusion of thickening agents such as gums or other forms of hydrophilic colloids. One preferred embodiment is an oil-in-water cream. Such compositions are referred to herein as dermally, dermatologically, or pharmaceutically acceptable carriers.

DETD [0019] Suitable carriers include water, alcohols, oils and the like, chosen for their ability to dissolve or disperse ingredients used in the treatment. In some embodiments, active and/or adjunct ingredients are added to a sunscreen or sunblock formulations so that topical application has the further advantage of preventing repigmentation during and/or after treatment. Preferred formulae of this type are SPF 15 or higher. Many of these preferred embodiments contain titanium

dioxide or zinc oxide which additionally soothe and lubricate the **skin** and help minimize side effects in sensitive **skin** and with formulations containing high concentrations of bleaching ingredients.

DETD [0020] Generally in the practice of methods of the invention, the composition is topically applied to darkened **skin** areas in a predetermined or as-needed regimen either at intervals by application of a lotion or the like, it generally being the case that gradual lightening is noted with each successive application. Insofar as has been determined based upon clinical studies to date, no adverse side effects are encountered. It is an advantage of the invention that it can be used to augment other **skin** lightening treatments including, but not limited to, those discussed above such as topical administration of hydroquinone, hydroquinone and glycolic acid, and kojic acid.

CLM What is claimed is:

1. A method for whitening **skin** comprising topically administering to the **skin** an effective amount of a composition containing from about 0.5% to about 25% by weight of an active ingredient selected from the group consisting of .alpha.-hydroxytetronic acid; .alpha.-hydroxytetronic acid substituted in the .gamma.-position with a C.sub.1 to C.sub.8 alkyl, C.sub.3 to C.sub.6 cycloaliphatic, phenyl, chlorophenyl, dichlorophenyl, tolyl, or phenethyl group; lower alkoxy derivatives; their lower alkyl esters and physiologically acceptable salts; and mixtures thereof.

9. A method for whitening **skin** comprising applying to the **skin** a composition containing an effective amount of .alpha.-hydroxytetronic acid and at least one adjunct ingredient selected from the group consisting of hydroquinone, an .alpha.-hydroxy acid, and a fatty acid ester of ascorbic acid.

13. A topical composition useful for whitening **skin** comprising a dermatologically acceptable carrier and (a) from about 0.5% to about 25% by weight of an active ingredient selected from the group consisting of .alpha.-hydroxytetronic acid; .gamma.-hydroxytetronic acid substituted in the .gamma.-position with a C.sub.1 to C.sub.8 alkyl, C.sub.3 to C.sub.6 cycloaliphatic, phenyl, chlorophenyl, dichlorophenyl, tolyl, or phenethyl group; lower alkoxy derivatives; their lower alkyl esters and physiologically acceptable salts; and mixtures thereof; and (b) from about 0.25% to about 25% by weight of at least one adjunct ingredient selected from the group consisting of hydroquinone, an .alpha.-hydroxy acid, and a fatty acid ester of ascorbic acid.

PI US 2002071816 A1 20020613
US 6417226 B2 20020709

L34 ANSWER 7 OF 15 USPATFULL

TI **SKIN** WHITENERS CONTAINING HYDROXYTETRONIC ACID

AB **Skin** whitening compositions contain .alpha.-hydroxytetronic acid or a .alpha.-hydroxytetronic derivative, and, in some cases, hydroquinone, an .alpha.-hydroxy acid such as glycolic acid, and a fatty acid ester of ascorbic acid such as ascorbyl palmitate.

SUMM [0003] This invention relates to the use of hydroxytetronic acid and/or hydroxytetronic acid derivatives alone, or in combination with other ingredients such as hydroquinone, glycolic acid, and/or ascorbyl palmitate, in compositions that whiten **skin**, and methods for using the compositions.

SUMM [0005] A variety of dermatological compositions have been suggested for **skin** whitening to improve the appearance of hyperpigmentary **skin** conditions such as that observed as freckles, melasma, cafe au lait and liver spots spots, and lesions observed in Addison's disease, hemochromatosis, vitiligo, piebald-ism, phenylketonuria, and the like, and/or for cosmetic purposes. **Skin** color is primarily determined by the amount of melanin present in epidermal cells, so many modern **skin** bleaching compositions either destroy melanin (typically by destroying or disrupting melanin granules) or inhibit its formation (often by inhibiting tyrosinase, a melanin biosynthetic enzyme, or melanocyte activity), or both. Many of these contain harsh chemicals such as peroxides, acids or formaldehyde, or thiolated materials such as glutathione, cysteine, mercaptosuccinic acid, mercaptodextran, and mercapto-ethanol, which have an objectionable odor that makes products containing them undesirable to a consumer (discussed in U.S. Pat. No. 5,980,904 to Leverett and Dornoff, 5,747,006 to Dornoff, et al., and 6,077,503 to Dornoff; these and subsequent references are hereby incorporated herein in their entireties by reference).

SUMM [0006] Less stringent therapies have other disadvantages. The only treatment for hyperpigmentation that is approved in the United States for use by consumers without a prescription, for example, is the topical application of hydroquinone, which acts by suppressing melanocyte activity. Hydroquinone is oxidized by air, light, and tyrosinase itself, however, which adversely effects the shelf life of preparations containing it and its bioavailability upon application. Hydroquinone can cause burning, redness, sensitization and irritation in some persons, particularly after application of quantities sufficient to cause **skin** bleaching as it requires prolonged treatment before results are noticeable, and its oxidized products have been implicated in **skin** irritation and pigmentation rebound (U.S. Pat. No. 6,068,834 to Kvalnes, et al.). Topical retinoids and topical corticosteroids have been suggested as hypopigmenting agents, as have laser treatment and chemical peels, but these fall short of desirable responses. A new combination therapy recently suggested combines tretinoin and fluocinolone with hydroquinone (Willis, I., **Skin** & Aging Supp., Nov. 2000, 17-21). Kojic acid and arbutin have also been suggested, but these are marginal tyrosinase inhibitors and are not very bioavailable and thus have disappointing efficacy.

SUMM [0007] Other pleasanter compositions recently suggested employ natural materials, which have in some cases been used for centuries in Asia or Europe to bleach **skin** and **skin** areas, or enhance the appearance of fair **skin**. These include the use of lemon, orange, cucumber, ginko, carob, rose fruit, geraniuim herb, cinnamon, sweet marjoram, rosemary, clove, mulberry, licorice, bearberry, and acerola cherry extracts (ibid.). The variability of active ingredients in these natural products sometimes limits their usefulness, particularly as **skin** type, color, age, and condition of vary greatly in different subjects, and make suggested dosages and regimens

difficult to fashion. And other ingredients in the mixtures can cause allergic reactions in sensitive persons.

SUMM [0008] It would be desirable to have alternative preparations, and/or ones that improve the efficacy of presently known **skin** whitening agents.

SUMM [0009] It is an objective of the invention to provide new compositions for whitening **skin** and methods for their use. It is a further objective to provide compositions that can be used to enhance known **skin** whitening compositions and treatments.

SUMM [0010] These objectives are achieved by the present invention, which provides methods and compositions for whitening **skin** through the topical application of .alpha.-hydroxytetronic acid and/or 60 -hydroxytetronic derivatives, in a preparation that typically includes a dermatologically acceptable carrier. In many embodiments, the .alpha.-hydroxytetronic active ingredient is applied to **skin** in **combination** with at least one adjunct ingredient such as **hydroquinone**, an .alpha.-hydroxy acid such as glycolic acid, and a fatty acid **ester** of **ascorbic** acid such as **ascorbyl** palmitate. Some preferred embodiments contain from about 0.5% to about 25% by weight .alpha.-hydroxytetronic acid and/or hydroxytetronic acid derivatives alone, or in **combination** with **hydroquinone**, glycolic acid and/or ascorbyl palmitate.

DETD [0011] This invention is based upon the finding that .alpha.-hydroxytetronic acid, alone or in combination with hydroquinone, provides significant bleaching when applied to the **skin**, without undesirable side effects.

DETD [0012] In the practice of the invention, a composition containing an effective amount of .alpha.-hydroxytetronic acid active ingredient, i.e., .alpha.-hydroxytetronic acid, a derivative, or mixtures thereof, is applied to **skin** to whiten it. By "whitening" is meant the visually apparent reduction in **skin** pigmentation observed qualitatively and sometimes measured using an assay such as Melanoderm in vitro assays that quantify changes in melanin formation in cultured mammalian epidermal cells. Alpha-hydroxytetronic acid (sometimes called 2-hydroxytetronic acid) may be thought of as ascorbic acid without a side chain; the enol form, 3,4-dihydroxy-2-(5H) furnanone, has the formula ##STR1##

DETD [0014] Typical compositions of the invention contain from about 0.5% to about 25% by weight, more narrowly from about 2% to about 15% by weight, and even more narrowly from about 3% to about 10% by weight, .alpha.-hydroxytetronic acid and/or a derivative thereof. Lower concentrations may be employed for less pronounced hyperpigmentation conditions and in sunscreens and sunblocks used after **skin** whitening treatment (more fully discussed below), and higher concentrations may be employed with more acute pigmentation conditions. Suggested ranges also depend upon any adjunct ingredients employed in the compositions (more fully discussed below) and the user's coloring and **skin** type as well as the extent of severity of the hyperpigmentation problem. Some embodiments contain from about 1% to 10%, more narrowly from about 2% to about 5%, even more narrowly from about 3% to about 4% by weight hydroxytetronic acid; others contain from about 7% to about 25%, more narrowly from about 10% to about 15%, by weight hydroxytetronic acid. As a practical matter, however, to avoid the need for repeated application, it is desirable that the topically applied composition be formulated to contain at least about 3 to 5% by weight hydroxytetronic acid, and many embodiments contain about 10% or higher.

DETD [0016] As used herein, the term ".alpha.-hydroxy acid" has reference to and encompasses the general class of organic compounds containing at least one hydroxy group and at least one carboxyl group, and wherein at

least one hydroxyl group is located on the .alpha.-carbon atom. Typically, the compounds are organic acids having at least one carboxylic acid group and at least one hydroxyl group on the .alpha.-carbon atom, and may contain other functional groups including additional hydroxyl and carboxylic acid moieties. Preferred .alpha.-hydroxy acids and/or .alpha.-hydroxy acid derivatives are those which are less bulky structurally, typically having a one- to three-carbon backbone, so that they penetrate the **skin** well such as those set out in U.S. Pat. No. 5,965,618 at column 6 lines 4 to 29. Where employed, glycolic and/or lactic acid or their derivatives are preferred; glycolic acid is especially efficacious. Lactic acid was suggested as a **skin**-whitening agent in U.S. Pat. No. 5,262,153 to Mashima, et al. Typical hydroxy acid concentrations range from about 1% to about 25% by weight, more narrowly from about 2% to about 15%, and even more narrowly from about 3% to 10% by weight. As with the hydroxytetronic acid ingredient, higher concentrations may be employed for more acute conditions. In some embodiments, for example, from about 8% to 12% may be employed; in others, ranges of from about 3% to about 7% by weight are sufficient. One efficacious composition of the invention contains about 10% hydroxytetronic acid, about 10% glycolic acid, and about 4% hydroquinone.

DETD [0017] Fat-soluble fatty acid **esters** of **ascorbic** acid (vitamin C) are employed as alternate or additional adjunct ingredients in other embodiments, alone or in **combination** with **hydroquinone** or .alpha.-hydroxy acids. The more oxidation-resistant saturated fatty acid **esters** of **ascorbic** acid are preferred, including, but not limited to, ascorbyl laurate, ascorbyl myristate, ascorbyl palmitate, ascorbyl stearate, and ascorbyl behenate. Ascorbyl palmitate is used in one embodiment. As denoted herein, where fatty acid esters are described, e.g., ascorbyl stearate, compositions having predominantly that ester, e.g., predominantly stearate, are included. The esters may be prepared using hydrogenated oils or fats, or fractions thereof, and contain small amounts of another ester. Ascorbyl stearate prepared using canola, for example, commonly contain about 4% ascorbyl palmitate. It is an advantage of the invention that where fatty acid esters of ascorbic acid are employed as an adjunct ingredient, they help provide emollient properties to the composition. Typical concentration ranges of ascorbyl palmitate vary from about 0.25% to about 10%, more narrowly from about 2% to about 8%, and even more narrowly from about 3% to about 5% by weight.

DETD [0018] However, only effective amounts of active ingredient(s) are needed to whiten **skin**, so generally topical application to **skin** sites is accomplished in association with a carrier, and particularly one in which the active ingredient is soluble per se or is effectively solubilized (e.g., as an emulsion or microemulsion). Where employed, the carrier is inert in the sense of not bringing about a deactivation or oxidation of active or adjunct ingredient(s), and in the sense of not bringing about any adverse effect on the **skin** areas to which it is applied. In one preferred practice of the invention, hydroxytetronic acids are applied in admixture with a dermatologically acceptable carrier or vehicle (e.g., as a lotion, cream, ointment, soap, stick, or the like) so as to facilitate topical application and, in some cases, provide additional beneficial effects as might be brought about, e.g., by moisturizing of the affected **skin** or mucosal areas. While the carrier for dermatological compositions can consist of a relatively simple solvent or dispersant such as water, it is generally preferred that the carrier comprise a composition more conducive to topical application, and particularly one which will form a film or layer on the **skin** to which it is applied so as to localize the application and provide some resistance to washing off by immersion in water or by perspiration and/or aid in the percutaneous delivery of the active agent. Many preparations are known in the art, and include lotions containing oils and/or alcohols and

emollients such as olive oil, hydrocarbon oils and waxes, silicone oils, other vegetable, animal or marine fats or oils, glyceride derivatives, fatty acids or fatty acid esters or alcohols or alcohol ethers, lecithin, lanolin and derivatives, polyhydric alcohols or esters, wax esters, sterols, phospholipids and the like, and generally also emulsifiers (nonionic, cationic or anionic), although some of the emollients inherently possess emulsifying properties. These same general ingredients can be formulated into a cream rather than a lotion, or into gels, or into solid sticks by utilization of different proportions of the ingredients and/or by inclusion of thickening agents such as gums or other forms of hydrophilic colloids. One preferred embodiment is an oil-in-water cream. Such compositions are referred to herein as dermally, dermatologically, or pharmaceutically acceptable carriers.

DETD [0019] Suitable carriers include water, alcohols, oils and the like, chosen for their ability to dissolve or disperse ingredients used in the treatment. In some embodiments, active and/or adjunct ingredients are added to a sunscreen or sunblock formulations so that topical application has the further advantage of preventing repigmentation during and/or after treatment. Preferred formulae of this type are SPF 15 or higher. Many of these preferred embodiments contain titanium dioxide or zinc oxide which additionally soothe and lubricate the **skin** and help minimize side effects in sensitive **skin** and with formulations containing high concentrations of bleaching ingredients.

DETD [0020] Generally in the practice of methods of the invention, the composition is topically applied to darkened **skin** areas in a predetermined or as-needed regimen either at intervals by application of a lotion or the like, it generally being the case that gradual lightening is noted with each successive application. Insofar as has been determined based upon clinical studies to date, no adverse side effects are encountered. It is an advantage of the invention that it can be used to augment other **skin** lightening treatments including, but not limited to, those discussed above such as topical administration of hydroquinone, hydroquinone and glycolic acid, and kojic acid.

CLM What is claimed is:

1. A method for whitening **skin** comprising topically administering to the **skin** an effective amount of a composition containing from about 0.5% to about 25% by weight of an active ingredient selected from the group consisting of .alpha.-hydroxytetronic acid; .alpha.-hydroxytetronic acid substituted in the .gamma.-position with a C.sub.1 to C.sub.8 alkyl, C.sub.3 to C.sub.6 cycloaliphatic, phenyl, chlorophenyl, dichlorophenyl, tolyl, or phenethyl group; lower alkoxy derivatives; their lower alkyl esters and physiologically acceptable salts; and mixtures thereof.

9. A method for whitening **skin** comprising applying to the **skin** a composition containing an effective amount of .alpha.-hydroxytetronic acid and at least one adjunct ingredient selected from the group consisting of hydroquinone, an .alpha.-hydroxy acid, and a fatty acid ester of ascorbic acid.

13. A topical composition useful for whitening **skin** comprising a dermatologically acceptable carrier and (a) from about 0.5% to about 25% by weight of an active ingredient selected from the group consisting of .alpha.-hydroxytetronic acid; .gamma.-hydroxytetronic acid substituted in the .gamma.-position with a C.sub.1 to C.sub.8 alkyl, C.sub.3 to C.sub.6 cycloaliphatic, phenyl, chlorophenyl, dichlorophenyl, tolyl, or phenethyl group; lower alkoxy derivatives; their lower alkyl esters and physiologically acceptable salts; and mixtures thereof; and (b) from about 0.25% to about 25% by weight of at least one adjunct ingredient selected from the group consisting of hydroquinone, an .alpha.-hydroxy acid, and a fatty acid ester of ascorbic acid.

PI US 2002071816 A1 20020613

retinol, Ceteareth-20

CLM What is claimed is:

24. A **skin** benefit composition comprising: hydroquinone; a cationic salt of acidic ascorbyl esters, and a protected retinoid, said composition having a pH of about 5.5 to about 8.0.

106. The process of making a stable **hydroquinone** composition having a pH of about 5.5 to about 8.0 comprising: **combining** the following ingredients, in a carbon dioxide atmosphere: first, magnesium **ascorbyl phosphate** and sodium metabisulfite, then second, sodium metabisulfite, then third, magnesium **ascorbyl phosphate**, then fourth, **hydroquinone**; and wherein said ingredients are contained in suitable dermatologically acceptable carriers.

PI US 2003053968 A1 20030320

L3 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2003 ACS

AB Populations of cytotoxic semiquinone and ascorbyl free radicals with half-lives in excess of 103 s result from the interaction of 2,6-dimethoxy-p-quinone [530-55-2] with ascorbic acid [50-81-7] at pH 7.4. Kinetics for these ascorbyl and semiquinone free radical populations have been detd. exptl. by ESR. Neither transition metals nor O were found to be involved in the generation or decay of these free radicals and no evidence for the formation of other more reactive species such as OH radicals could be found by spin trapping. A theor. model is presented that accounts for the obsd. prodn. of free radicals and their kinetics. The formation and decay of semiquinone radicals can be explained by a conproportionation-disproportionation pseudoequil. existing between quinone and **hydroquinone** in the reaction mixt. The presence of **ascorbyl** cannot be explained in this way, however, and these radicals apparently result from one electron redn. of quinone by **ascorbate**. Criteria for the selection of other pairs of electron donors and acceptors capable of **synergistic** prodn. of long-lived free radical populations for applications such as chemotherapy are discussed.

L3 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2003 ACS

AB The skin conditioners, which show **synergistic** skin-lightening effect and prevent and treat rough skin, contain (a) .gtoreq.1 skin-lightening agents selected from **hydroquinone** glycosides, alkoxysalicylic acids, and their salts, (b) .gtoreq.1 betaines selected from R1N+Me2CH2CO2- (R1 = C8-24 linear or branched alkyl), imidazolinium betaines I (R2 = C7-23 linear or branched alkyl), R3CONH(CH2)3N+Me2CH2Co- (R3 = C7-23 linear or branched alkyl), and R4N+Me2CH2CH(OH)SO3- (R4 = C8-24 linear or branched alkyl), (c) fatty acids, and (d) .gtoreq.1 selected from L-serine, D-serine, DL-serine, alanine, trimethylglycine, and aminomethylpropanediol. (a) may be .alpha.-glycosyl-L-**ascorbic** acid. A lotion was prepd. from arbutin, L-serine, oleic acid, N-lauryl-N,N-dimethylaminoacetic acid, KOH, EtOH, and H2O and evaluated.

iminished spots and freckles in female volunteers.

L3 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2003 ACS

AB Skin-lightening cosmetics contain L-**ascorbic** acid (including salts or derivs., excluding **ascorbic** acid glycosides), hinokitiol (derivs.), 2-hydroxycarboxylic acids (including salts or derivs.), **hydroquinone** (derivs.), cysteine (derivs.), glucosamine (derivs.), azelaic acid (derivs.), placenta exts., and/or melanin formation-inhibiting exts. of plants or algae and Gentiana exts. A cosmetic lotion contg. 0.10 wt.% L-**ascorbic** acid phosphate Mg salt and 0.5 wt.% G. lutea ext. showed **synergistic** skin-lightening effect.

L32 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2003 ACS

AB In **combination** with **hydroquinone** at pH 4.0 ascorbyl palmitate (I) showed some beneficial effect, but ascorbic acid (II), thioglycolic acid (III), and Na bisulfite (IV) were detrimental. With diphenyl-p-phenylenediamine as a primary autoxidant I and II had a protective effect, but III and IV were detrimental. Glycine and alanine had adverse effects on **hydroquinone** (V), butylated hydroxyanisole (VI), and nordihydroguaiaretic acid (VII). Phosphoric, maleic, malonic, citric, tartaric, and malic acids had small pos. or neg. effects on V, VI, and VII, but had strong synergistic effects on phenyl-1-naphthylamine and diphenyl-p-phenylenediamine in slightly acidic soln., as had also malonic acid, ascorbic acid, and ascorbyl palmitate. On V, VI, and VII thioglycolic acid and Na bisulfite were detrimental in alk. soln. Only glycine and citric acid showed any influence on diarylamine antioxidants.

IT Palmitic acid, **ester** with **ascorbic** acid
(as antioxidant synergist with amines and phenols in Me linoleate-H2O system)

ACCESSION NUMBER: 1960:94633 CAPLUS
DOCUMENT NUMBER: 54:94633
ORIGINAL REFERENCE NO.: 54:17918c-e
TITLE: Comparison of some synergistic antioxidants in a methyl linoleate-water system
AUTHOR(S): Spetsig, Lars Olov
SOURCE: Arkiv Kemi (1959), 15, 23-30
DOCUMENT TYPE: Journal
LANGUAGE: English

L17 ANSWER 12 OF 51 USPATFULL

DETD In another embodiment of the invention an outer layer of skin may be removed before the skin is exposed to an active agent or ultrasound. This tends to enable the active agent to penetrate better and/or deeper. This may be achieved, for example, by first wiping the skin with acetone to strip the oils out. An enzyme may then be used to selectively kill only dead skin cells. Pretreatment with heat, skin hydrating preparations and preparations to alter (and optimize for treatment) the skin **pH** may also be utilized. Chemicals, abraders and lasers may also be used for this purpose, although they tend to be less discriminate. An active agent may then be placed on the skin and exposed to ultrasound, or the skin may be exposed to ultrasound prior to placing an active agent on the skin. The active agent may then be wiped off. The barrier function of the outer skin layer tends to return within a few hours or days.

DETD Examples of the active agent might include any of the following, either alone or in **combination**: Vitamin C; Vitamin E; Vitamin A; Vitamin K; Vitamin F; any of the various chemical forms and analogs of these vitamins; Retin A (Tretinoin); Adapalene; Retinol; **Hydroquinone**; Kojic acid; various growth factors; echinacea; antibiotics; antifungals; antivirals; bleaching agents: alpha hydroxy acids; beta hydroxy acids; salicylic acid; antioxidant triad compound (with or without Tretinoin or Vitamin A derivatives); seaweed and salt water derived products antioxidants, phytoanthocyanims, phytonutrients, botanical and herbaceous products, hormones (including insulin or estrogens), enzymes, minerals, growth factors, genetically engineered substances, cofactors or catalysts for various biological pathways and other antiaging substances.

DETD Molecular Size--The active agent should preferably have a molecular size which enables it to penetrate the skin at the time of maximum permeability, and then should preferably be in a form which is either "active" or may become "activated" in the skin. For example, in the case of Vitamin C treatments, L-ascorbic acid has stability problems but is the active form in the skin and is a small molecule which enables penetration. In contrast, **magnesium ascorbyl** phosphate is very stable but is a much larger molecule and does not penetrate easily with current delivery systems. Guy & Potts have shown that the permeability of human (and mouse) stratum corneum may be determined by the molecular volume (weight) and the partition coefficient log poor.

DETD **pH**--The activity of an active agent may frequently depend on an appropriate **pH** level. It is also important for skin to be at an optimal **pH** level. There is good evidence that the stratum corneum is much more permeable to neutral molecules than the salts of the weak acids or bases. Furthermore, skin enzymes and other processes may operate optimally at certain **pH** levels and poorly at others. For example, an enzyme preparation used to remove stratum corneum may operate effectively at a **pH** level of 8.5. The skin may preferably be "pretreated" with a topical agent that increases the **pH** of the skin to this level. At the end of the treatment it may be advantageous to add another topical buffering solution or agent to "readjust" the skin back down to a normal skin **pH** level of 5.5.

DETD pKa--The pKa tends to affect the amount of free acid and base in equilibrium, and thus has an impact on both the beneficial and adverse clinical effects of the active agent. A recent study by the FDA has shown that there may be considerable variation in the beneficial clinical effects (as well as the adverse and undesirable clinical side effects) of glycolic acid, even when the glycolic acid concentrations are the identical percentage. For example, if the **pH** of the glycolic acid preparation is adjusted to around 4.4 (approximately equal to the pKa of glycolic acid), then the ratio of beneficial to adverse side effects is much better than when the **pH** is lower than the

pKa (and more free acid is available in the equilibrium). The pKa may vary for different compounds and thus may effect the choice of formulation.

DETD A sterile unpreserved unit dose package, vial, twist off plastic, tear packet, etc. type of container which contains a solution that adjusts the **pH** of the skin to **pH** 8.5

DETD A vial of dry enzyme powder (which requires **pH** 8.5 to properly function).

DETD A buffering solution to restore the skin to **pH** 5.5 (if necessary for a given process or active agent).

PI US 6030374 20000229

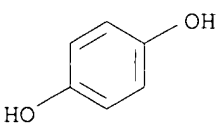
L4 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2003 ACS
AN 1987:121882 CAPLUS
DN 106:121882
TI Dry bleach-stable enzyme composition
IN Herdeman, Robert William
PA Procter and Gamble Co., USA
SO Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C11D003-386
ICS C11D003-39
CC 46-5 (Surface Active Agents and Detergents)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 206417	A2	19861230	EP 1986-201054	19860618
	EP 206417	A3	19881109		
	R: BE, DE, FR, GB, IT, LU, NL				
	US 4707287	A	19871117	US 1985-750715	19850628
	AU 8659320	A1	19870108	AU 1986-59320	19860627
	AU 579553	B2	19881124		
	JP 62079298	A2	19870411	JP 1986-151358	19860627
	CA 1285509	A1	19910702	CA 1986-512636	19860627
PRAI	US 1985-750715		19850628		

AB **Water-sol**. granules are prepd. which comprise a core of an enzyme-contg. material and a protective coating contg. an alk. buffer salt having a pH of 7-11. The granules exhibit good retention of enzyme activity during storage in contact with granules of solid peroxy acid bleach. The coating optionally contains an **antioxidant** (e.g., NaHSO3 or Na2SO3), CaCl2, and other inorg. salts as well as overcoatings of **water-sol**. waxy nonionic material and alk. soln.-sol. acetate phthalate resin. Fluidized enzyme-contg. particles (T-granulate, 800 g) were sprayed with 1000 g aq. soln. (at 70.degree.) contg. 200 g KHCO3 and 40 g Na sulfite and dried to prep. coated granules which (800 g) were fluidized and sprayed with 200 g ethoxylated (22 mol) tallow alc. at 55.degree. and cooled to prep. granules for use with solid peroxy acid bleach granules in detergent compns.

ST enzyme coating bleach resistance; buffer salt coating enzyme; potassium bicarbonate coating enzyme; **antioxidant** sulfite stability

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 123-31-9 REGISTRY
CN 1,4-Benzenediol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Hydroquinone (8CI)**
OTHER NAMES:
CN 1,4-Benzoquinol
CN 1,4-Dihydroxybenzene
CN 4-Hydroxyphenol
CN Aida
CN Arctuvin
CN Benzohydroquinone
CN Benzoquinol
CN Black & White Bleaching Cream
CN BQ(H)
CN Diak 5
CN Dihydroquinone
CN Eldopacque
CN Eldopaque
CN Eldopaque Forte
CN Eldoquin
CN Eldoquin Forte
CN HE 5
CN Hydroquinol
CN p-Benzenediol
CN p-Dihydroquinone
CN p-Dihydroxybenzene
CN p-Dioxybenzene
CN p-Hydroquinone
CN p-Hydroxyphenol
CN p-Phenylenediol
CN p-Quinol
CN Phiaquin
CN Quinol
CN Solaquin Forte
CN Tecquinol
CN Tenox HQ
FS 3D CONCORD
DR 8027-02-9, 57534-13-1
MF C6 H6 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16590 REFERENCES IN FILE CA (1962 TO DATE)
677 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
16609 REFERENCES IN FILE CAPLUS (1962 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

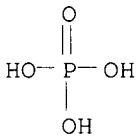
=> s magnesium ascorbyl phosphate/cn
L2 1 MAGNESIUM ASCORBYL PHOSPHATE/CN

=> d

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 108910-78-7 REGISTRY
CN L-Ascorbic acid, phosphate, magnesium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Ascorbic acid phosphate magnesium salt
CN C-Mate
CN Magnesium ascorbate phosphate
CN **Magnesium ascorbyl phosphate**
CN Magnesium L-ascorbate phosphate
FS STEREOSEARCH
DR 224960-02-5
MF C6 H8 O6 . x H3 O4 P . x Mg
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CEN, CHEMCATS, CSCHEM, TOXCENTER, USPATFULL

CM 1

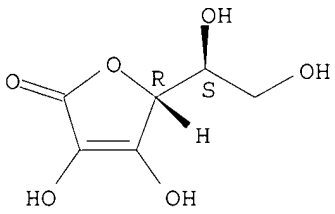
CRN 7664-38-2
CMF H3 O4 P



CM 2

CRN 50-81-7
CMF C6 H8 O6

Absolute stereochemistry.



298 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
299 REFERENCES IN FILE CAPLUS (1962 TO DATE)

(FILE 'HOME' ENTERED AT 15:47:13 ON 15 APR 2003)

FILE 'REGISTRY' ENTERED AT 15:47:21 ON 15 APR 2003
L1 1 S HYDROQUINONE/CN
L2 1 S MAGNESIUM ASCORBYL PHOSPHATE/CN

FILE 'CAPLUS, EMBASE, SCISEARCH, USPATFULL' ENTERED AT 15:50:05 ON 15 APR 2003
L3 1465 FILE CAPLUS
L4 452 FILE EMBASE
L5 664 FILE SCISEARCH
L6 2138 FILE USPATFULL
TOTAL FOR ALL FILES
L7 4719 S HYDROQUINONE1 OR 4-BENZOQUINO1 OR 4-DIHYDROXYBENZENE OR 4-HYD
L8 4482 FILE CAPLUS
L9 635 FILE EMBASE
L10 1095 FILE SCISEARCH
L11 6228 FILE USPATFULL
TOTAL FOR ALL FILES
L12 12440 S HYDROQUINONE1 OR 4-BENZOQUINO OR DIHYDROXYBENZENE OR 4-HYDROX
L13 16625 FILE CAPLUS
L14 1906 FILE EMBASE
L15 0 FILE SCISEARCH
L16 1928 FILE USPATFULL
TOTAL FOR ALL FILES
L17 20459 S L1
L18 16625 FILE CAPLUS
L19 1906 FILE EMBASE
L20 2 FILE SCISEARCH
L21 8 FILE USPATFULL
TOTAL FOR ALL FILES
L22 18541 S 123-31-9
L23 16061 FILE CAPLUS
L24 0 FILE EMBASE
L25 0 FILE SCISEARCH
L26 1928 FILE USPATFULL
TOTAL FOR ALL FILES
L27 17989 S 123-31-9/RN
L28 16625 FILE CAPLUS
L29 1906 FILE EMBASE
L30 2 FILE SCISEARCH
L31 1933 FILE USPATFULL
TOTAL FOR ALL FILES
L32 20466 S L22 OR L27 OR L17
L33 269 FILE CAPLUS
L34 13 FILE EMBASE
L35 14 FILE SCISEARCH
L36 254 FILE USPATFULL
TOTAL FOR ALL FILES
L37 550 S ASCORBIC ACID PHOSPHATE MAGNESIUM OR C-MATE OR MAGNESIUM ASCO
L38 339 FILE CAPLUS
L39 13 FILE EMBASE
L40 14 FILE SCISEARCH
L41 268 FILE USPATFULL
TOTAL FOR ALL FILES
L42 634 S L2 OR L37
L43 299 FILE CAPLUS
L44 0 FILE EMBASE
L45 0 FILE SCISEARCH
L46 0 FILE USPATFULL
TOTAL FOR ALL FILES
L47 299 S 108910-78-7
L48 298 FILE CAPLUS

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L49             0 FILE EMBASE
L50             0 FILE SCISEARCH
L51            42 FILE USPATFULL
     TOTAL FOR ALL FILES
L52           340 S 108910-78-7/RN
L53           339 FILE CAPLUS
L54            13 FILE EMBASE
L55            14 FILE SCISEARCH
L56           268 FILE USPATFULL
     TOTAL FOR ALL FILES
L57           634 S L52 OR L42
L58            37 FILE CAPLUS
L59             1 FILE EMBASE
L60             0 FILE SCISEARCH
L61            13 FILE USPATFULL
     TOTAL FOR ALL FILES
L62            51 S L57 AND L32
L63            15 FILE CAPLUS
L64             0 FILE EMBASE
L65             0 FILE SCISEARCH
L66            13 FILE USPATFULL
     TOTAL FOR ALL FILES
L67            28 S L62  AND (COMPOSITION OR PREPARATION)

=> s l67 and "ph"
L68            2 FILE CAPLUS
L69            0 FILE EMBASE
L70            0 FILE SCISEARCH
L71            8 FILE USPATFULL

TOTAL FOR ALL FILES
L72           10 L67 AND "PH"
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Ascorbic + Hydroquinone

L72 ANSWER 8 OF 10 USPATFULL

SUMM In another embodiment, the present invention involves a topical skin exfoliation **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid. It may further comprise hydroquinone. In one embodiment, the **composition** is 16-14 parts L+ lactic acid, 18-24 parts citric acid, 2 parts kojic acid and 50 to 65 parts ethyl alcohol. A preferred topical skin exfoliation **composition** useful in skin peels involves 10-16 parts L+ lactic acid, 12-18 parts citric acid, 14 parts salicylic acid, 2 parts kojic acid and 50 to 65 parts ethyl alcohol.

SUMM a) obtaining a **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid;

SUMM b) applying a coating of said **composition** to the facial skin in an amount effective to cause skin peeling.

SUMM a) prior to applying said **composition**, thoroughly cleansing facial skin to be exfoliated using an appropriate degreaser;

SUMM b) applying a second coat of said **composition** to the facial skin 2 to 4 minutes after the first coat;

SUMM c) applying third and further coats of said **composition** to the facial skin at 2 to 4 minute intervals until appearance of crystals or "frosting";

SUMM None before have prepared a **composition** according to the present invention for the use of a superior skin exfoliation or peeling **composition**. Of course, neither has such **composition** been used in a method for such a procedure.

DETD Glycolic acid has the smallest molecule of the alpha hydroxy acids allowing for enhanced penetration into the dermal layers when conditions warrant. It is commercially available as a white crystalline compound that is 99% pure and also as a 70% aqueous solution. Preferred embodiments include addition of kojic acid and derivatives thereof along with additional components such as hydroquinone in the 1 to 2% range. Skin response to glycolic acid depends not only on its concentration and **pH** but also on other factors such as the amount of free acid delivered to the skin, the duration of contact, **preparation** of the skin before peeling, and the condition of the skin before treatment.

DETD The effect of the skin peeling treatment with and without hydroquinone was tested by comparative application of the method. In this example the subjects were directed to wash both arms with cleanser, consisting of acetone. The arms were then cleaned with a balancing toner. Then, four successive coats of the skin peeling **composition**, consisting of Example 3 were applied. Subjects were then directed to wipe off the dried film with more toner and to apply sunscreen to protect the treated skin. This was followed by a twice-daily regiment of wash, toner, and sunscreen.

DETD All of the **compositions** and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the **compositions** and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the **compositions** and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled

in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

CLM What is claimed is:

1. A therapeutic skin peel **composition** comprising a melanin inhibitor in combination with a hydroxy acid.

2. The **composition** of claim 1, wherein said melanin inhibitor comprises kojic acid or a derivative thereof.

3. The **composition** of claim 1, wherein said hydroxy acid is selected from the group consisting of an .alpha.-hydroxy acid, a .beta.-hydroxy acid or a keto acid.

4. The **composition** of claim 1, wherein said combination is in an ethyl alcohol/water carrier.

5. The **composition** of claim 3, wherein said .alpha.-hydroxy acid is selected from the group consisting of L-lactic acid, glycolic acid, tartaric acid and malic acid.

6. The **composition** of claim 3, wherein said .beta.-hydroxy acid is citric acid or L-ascorbic acid.

7. The **composition** of claim 3, wherein said keto acid is selected from the group consisting of L-ascorbic acid, salicylic acid and pyravic acid.

8. The **composition** of claim 5, wherein said .alpha.-hydroxy acid is malic acid.

9. The **composition** of claim 8, further comprising citric acid.

10. The **composition** of claim 9, further comprising a compound selected from the group consisting of hydroquinone, hydroquinone monobenzyl ether, and hydroquinone monoethyl ether.

11. The **composition** of claim 5, wherein said .alpha.-hydroxy acid is L-lactic acid.

12. The **composition** of claim 11, further comprising a .beta.-hydroxy acid.

13. The **composition** of claim 12, wherein said .beta.-hydroxy acid is citric acid.

14. The **composition** of claim 13, comprising 16 to 24 parts L(+) lactic acid, 18-24 parts citric acid and 2 parts kojic acid.

15. The **composition** of claim 12, further comprising a keto acid.

16. The **composition** of claim 15, wherein said keto acid is salicylic acid.

17. The **composition** of claim 16, comprising 10 to 16 parts L(+) lactic acid, 12 to 18 parts citric acid, 14 parts salicylic acid and 2 parts kojic acid.

18. A therapeutic skin peeling **composition** comprising at least one skin exfoliating agent and at least one melanin-inhibiting agent.

19. The **composition** of claim 18, further comprising at least one melanin bleaching agent.

20. The **composition** of claim 18, wherein said skin exfoliating agent is selected from the group consisting of salicylic acid, glycolic acid, retinoic acid, resorcinol, and pyruvic acid.

21. The **composition** of claim 20, wherein said skin exfoliating agent is glycolic acid.

22. The **composition** of claim 20, wherein said melanin-inhibiting agent is selected from the group consisting of gamma-L-glutamyl-L cysteine, gamma-L-cysteine, oxidized glutathione, polyphenol, linoleic acid, ellagic acid, glycyrrhizic acid, alkylsalicylic acid, kojic acid glycosides, kojic acid succinimide ester, thiazoles, propionic acid, sulphur, kojic acid, ascorbates and urea, L-ascorbate, kudzu roots, lavanols, caffeic acid, dicaffeoylquinic acid, tricaffeoylquinic acid, vitamin K, **ascorbic acid phosphate magnesium** salt, kojic acid dimer, hydantoin, tranexamic acid, chromone derivative, indomethicin methacin, erthorbic acid glucoside, phenol (in low concentration), niacinimide, cinnamic acid, conchiolin hydrolyzate, licorice root extract, hydroquinone, logwood extract, gromwell seed extract, arbutin, chitosans, superoxide dismutase, melanostatin, S-lactoyl glutathione, cystamine, buthionine sulfoximine, Feldamycin, glycyrrhetinic acid, phenylthioruea, glucosamine, ferulic acid, fuzi acid derived from conitum root, 5,6-dihydroxyindole, arginine, benzophenone, lysine and/or its derivatives, polylysine, linoleic acid, magnesium ascorbate, S-lactoyl glutathione, and hydroquinone glycoside.

23. The **composition** of claim 22, wherein said melanin-inhibiting agent is kojic acid.

24. The **composition** of claim 23, wherein said skin exfoliating agent is glycolic acid.

25. The **composition** of claim 23, wherein said skin exfoliating agent is salicylic acid.

26. The **composition** of claim 19, wherein said melanin bleaching agent is selected from the group consisting of citric acid, lactic acid, ascorbic acid, and azelaic acid.

27. The **composition** of claim 19, wherein said melanin bleaching agent may also act as a melanin-inhibiting agent.

28. The **composition** of claim 27, wherein said melanin bleaching agent is selected from the group consisting of arbutin, kojic acid, hydroquinone, superoxide dismutase, and gromwell seed extract.

29. The **composition** of claim 26, wherein said skin exfoliating agent is salicylic acid.

30. The **composition** of claim 29, wherein said melanin-inhibiting agent is kojic acid.

31. The **composition** of claim 30, futher comprising citric acid, lactic acid and ascorbic acid.

32. The **composition** of claim 31, comprising 10 to 16 parts L-lactic acid, 12 to 18 parts citric acid, 14 parts salicylic acid, 2 parts kojic acid and 2 parts ascorbic acid.

33. The **composition** of claim 18, further comprising at least one skin-penetrating agent.

34. The **composition** of claim 33, wherein said skin-penetrating

is selected from the group consisting of urea, aloe vera, casein, lactic acid and an .alpha.-hydroxy mixture.

35. A method for facial exfoliation comprising (a) obtaining a therapeutic skin peeling **composition** comprising kojic acid or a derivative thereof and at least one acid selected from the group consisting of an .alpha.-hydroxy acid, a .beta.-hydroxy acid, and a keto acid in an ethyl alcohol/water carrier; (b) applying a first coating of said **composition** to the facial skin in a manner effective to cause skin peeling; and (c) cleansing facial skin with water.

36. The method of claim 35, further comprising thoroughly cleansing facial skin prior to first application of said **composition** with a degreaser.

38. The method of claim 35, further comprising applying a second coating of said **composition** 2 to 4 minutes after first application of said **composition**.

39. The method of claim 36, further comprising applying a second coating of said **composition** 2 to 4 minutes after first application of said **composition**.

40. The method of claim 38, further comprising applying additional coatings of said **composition** 2 to 4 minutes after the previous application as needed until the appearance of crystals or "frosting".

41. The method of claim 39, further comprising applying additional coatings of said **composition** 2 to 4 minutes after the previous application as needed until the appearance of crystals or "frosting".

IT 50-81-7, Ascorbic acid, biological studies 51-85-4, Cystamine 52-90-4, L-Cysteine, biological studies 53-86-1, Indomethacin 56-87-1, L-Lysine, biological studies 57-13-6, Urea, biological studies 60-33-3, Linoleic acid, biological studies 64-17-5, Ethanol, biological studies 69-72-7, Salicylic acid, biological studies 74-79-3, L-Arginine, biological studies 77-92-9, Citric acid, biological studies 79-09-4, Propionic acid, biological studies 98-92-0, Niacinamide 103-85-5, Phenylthiourea 108-46-3, Resorcinol, biological studies 108-95-2, Phenol, biological studies 119-61-9, Benzophenone, biological studies **123-31-9**, Hydroquinone, biological studies 123-99-9, Azelaic acid, biological studies 302-79-4, Retinoic acid 331-39-5, Caffeic acid 461-72-3, Hydantoin 471-53-4, Glycyrrhetinic acid 476-66-4, Ellagic acid 491-38-3D, Chromone, derivs. 497-76-7, Arbutin 501-30-4D, Kojic acid, succinimide ester 621-82-9, Cinnamic acid, biological studies 1135-24-6, Ferulic acid 1182-34-9, Dicaffeoylquinic acid 1197-18-8, Tranexamic acid 1405-86-3, Glycyrrhizic acid 3131-52-0, 5,6-Dihydroxyindole 3416-24-8, Glucosamine 5072-26-4, Buthionine sulfoximine 5466-77-3, Octyl p-methoxycinnamate 7704-34-9, Sulfur, biological studies 9012-76-4, Chitosan 9054-89-1, Superoxide dismutase 9083-38-9, Melanostatin 12001-79-5, Vitamin K 13463-67-7, Titania, biological studies 15431-40-0, Magnesium ascorbate 25104-18-1, Polylysine 25138-66-3, S-Lactoylglutathione 27025-41-8, Oxidized glutathione 38000-06-5, Polylysine 56328-22-4 61230-27-1, Feldamycin **108910-78-7** 124134-09-4 154160-11-9
(.alpha.-hydroxy acid-kojic acid skin peel)

ACCESSION NUMBER: 2001:173623 USPATFULL
TITLE: Hydroxy-kojic acid skin peel
INVENTOR(S): Ancira, Margaret, 6850 N. 83rd St., Scottsdale, AZ, United States 85250

NUMBER	KIND	DATE

PATENT INFORMATION: US 6300369 B1 20011009

APPLICATION INFO.: US 1999-299788 19990222 (9)
RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-795231, filed on 10 Feb 1997, now patented, Pat. No. US 5874463
Continuation-in-part of Ser. No. U

16. A topical exfoliation **composition** comprising at least one skin exfoliating agent selected from the group consisting of salicylic acid; glycolic acid, retinoic acid; resorcinol, and pyruvic acid and at least one melanin-inhibiting agent selected from the group consisting of gamma-L-glutamyl-L cystine, gamma-L-cysteine, oxidized glutathione, polyphenol, linoleic acid, ellagic acid, glycyrrhizic acid, alkylsalicylic acid, kojic acid glycosides, kojic acid succinimide ester, thiazoles, propionic acid, sulphur, kojic acid, ascorbates and urea, L-ascorbate, kudzu roots, lavanols, caffeic acid, dicaffeoylquinic acid, tricaffeoylquinic acid, vitamin K, **ascorbic acid phosphate magnesium** salt, kojic acid dimer, hydantoin, tranexamic acid, chromone derivative, indomethicin methacin, erthorbic acid glucoside, phenol (in low concentration), niacinimide, cinnamic acid, conchiolin hydrolyzate, licorice root extract, hydroquinone, logwood extract, gromwell seed extract, arbutin, chitosans, superoxide dismutase, melanostatin, S-lactoyl glutathione, cystamine, buthionine sulfoximine, Feldamycin, glycyrrhetinic acid, phenylthiourea, glucosamine, ferulic acid, fuzi acid derived from aconitum root, 5. 6-dihydroxyindole, arginine, benzophenone, lysine and/or its derivatives, polylysine, linoleic acid, magnesium ascorbate, S-lactoyl glutathione, and hydroquinone glycoside.

16. A topical exfoliation **composition** comprising at least one skin exfoliating agent selected from the group consisting of salicylic acid; glycolic acid, retinoic acid; resorcinol, and pyruvic acid and at least one melanin-inhibiting agent selected from the group consisting of gamma-L-glutamyl-L cystine, gamma-L-cysteine, oxidized glutathione, polyphenol, linoleic acid, ellagic acid, glycyrrhizic acid, alkylsalicylic acid, kojic acid glycosides, kojic acid succinimide ester, thiazoles, propionic acid, sulphur, kojic acid, ascorbates and urea, L-ascorbate, kudzu roots, lavanols, caffeic acid, dicaffeoylquinic acid, tricaffeoylquinic acid, vitamin K, **ascorbic acid phosphate magnesium** salt, kojic acid dimer, hydantoin, tranexamic acid, chromone derivative, indomethicin methacin, erthorbic acid glucoside, phenol (in low concentration), niacinimide, cinnamic acid, conchiolin hydrolyzate, licorice root extract, hydroquinone, logwood extract, gromwell seed extract, arbutin, chitosans, superoxide dismutase, melanostatin, S-lactoyl glutathione, cystamine, buthionine sulfoximine, Feldamycin, glycyrrhetinic acid, phenylthiourea, glucosamine, ferulic acid, fuzi acid derived from aconitum root, 5. 6-dihydroxyindole, arginine, benzophenone, lysine and/or its derivatives, polylysine, linoleic acid, magnesium ascorbate, S-lactoyl glutathione, and hydroquinone glycoside.

17. The **composition** of claim 16 further defined as comprising at least one skin-penetrating agent selected from the group consisting of urea, aloe vera, casein, lactic acid, and an alpha hydroxy acid mixture.

18. The **composition** of claim 16 further defined as comprising at least one melanin bleaching agent selected from the group consisting of citric acid, lactic acid, ascorbic acid, arbutin, kojic acid, hydroquinone, superoxide dismutase, gromwell seed extract, and azelaic acid wherein some of the melanin bleaching agents also act as inhibitors for melanin formation.

IT 50-81-7, Ascorbic acid, biological studies 51-85-4, Cystamine 52-90-4, L-Cysteine, biological studies 53-86-1, Indomethacin 56-87-1, L-Lysine, biological studies 57-13-6, Urea, biological studies 60-33-3, Linoleic acid, biological studies 64-17-5, Ethanol, biological studies 69-72-7, Salicylic acid, biological studies 74-79-3, L-Arginine, biological studies 77-92-9, Citric acid, biological studies 79-09-4, Propionic acid, biological studies 98-92-0, Niacinamide 103-85-5, Phenylthiourea 108-46-3, Resorcinol, biological studies 108-95-2, Phenol, biological studies 119-61-9, Benzophenone, biological studies **123-31-9**, Hydroquinone, biological studies 123-99-9, Azelaic acid, biological studies 302-79-4, Retinoic acid 331-39-5, Caffeic acid 461-72-3, Hydantoin 471-53-4, Glycyrrhetinic acid 476-66-4, Ellagic acid 491-38-3D, Chromone, derivs. 497-76-7, Arbutin 501-30-4D, Kojic acid, succinimide ester 621-82-9, Cinnamic acid, biological studies 1135-24-6, Ferulic acid 1182-34-9, Dicaffeoylquinic acid 1197-18-8, Tranexamic acid 1405-86-3, Glycyrrhizic acid 3131-52-0, 5,6-Dihydroxyindole 3416-24-8, Glucosamine 5072-26-4, Buthionine sulfoximine 5466-77-3, Octyl p-methoxycinnamate 7704-34-9, Sulfur, biological studies 9012-76-4, Chitosan 9054-89-1, Superoxide dismutase 9083-38-9, Melanostatin 12001-79-5, Vitamin K 13463-67-7, Titania, biological studies 15431-40-0, Magnesium ascorbate 25104-18-1, Polylysine 25138-66-3, S-Lactoylglutathione 27025-41-8, Oxidized glutathione 38000-06-5, Polylysine 56328-22-4 61230-27-1, Feldamycin **108910-78-7** 124134-09-4 154160-11-9
(.alpha.-hydroxy acid-kojic acid skin peel)

ACCESSION NUMBER: 1999:24681 USPATFULL
TITLE: Hydroxy-kojic acid skin peel
INVENTOR(S): Ancira, Margaret, 6850 N. 83rd St., Scottsdale, AZ,

United States 85250

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5874463		19990223
APPLICATION INFO.:	US 1997-795231		19970210 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-328006, filed on 24 Oct 1994, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lambkin, Deborah C.
LEGAL REPRESENTATIVE: Arnold White & Durkee
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 613

L15 ANSWER 13 OF 14 USPATFULL
ACCESSION NUMBER: 74:59270 USPATFULL
TITLE: STABILIZATION OF HYDROQUINONE SOLUTIONS WITH CITRIC ACID
INVENTOR(S): Weris, III, Arthur P., Kingsport, TN, United States
PATENT ASSIGNEE(S): Eastman Kodak Company, Rochester, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 3855150		19741217
APPLICATION INFO.:	US 1973-344806		19730326 (5)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1970-46521, filed on 15 Jun 1970, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Padgett, Benjamin R.
ASSISTANT EXAMINER: Gluck, Irwin
LEGAL REPRESENTATIVE: Stevens, John F., Quillen, Jr., Cecil D.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 156
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Solutions of **hydroquinone** are **stabilized** against deterioration in color and odor with age by the addition to the solution of small amounts of citric acid. Up to about 1 percent citric acid by weight of the solution may be used, although it is preferred that this amount be between 0.005 percent and 0.05 percent.

CLM What is claimed is:

1. The method of stabilizing hydroquinone solutions comprising hydroquinone and a solvent therefor, said solvent being substantially free from impurities, against the formation of undesirable color and odor during storage which comprises adding to said solution from about 0.0025 percent

2. The method according to claim 1 which comprises adding to said solution between about 0.005 percent and about 0.05 percent by weight of the

3. The method of stabilizing solutions consisting essentially of hydroquinone and a solvent therefor selected from the group consisting of ethylene glycol, diethylene glycol and methoxyethanol against the formation of undesirable color and odor during storage which comprises adding to said solution from about 0.0025 percent to about 1 percent by

4. The method according to claim 3 which comprises adding to said solution between about 0.005 percent and about 0.05 percent, by weights of the

5. The method of stabilizing hydroquinone solutions consisting essentially of hydroquinone and methoxyethanol against the formation of undesirable color and odor during storage which comprises adding to said solution from about 0.0025 percent to about 1 percent by weight of the solution of citric acid.

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L18 ANSWER 20 OF 44 USPATFULL
ACCESSION NUMBER: 96:101605 USPATFULL
TITLE: Method of treating wrinkles using mandelic acid
INVENTOR(S): Yu, Ruey J., Ambler, PA, United States
Van Scott, Eugene J., Abington, PA, United States
PATENT ASSIGNEE(S): Tristrata Technology, Inc., Wilmington, DE, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5571841		19961105
APPLICATION INFO.:	US 1995-470434		19950606 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-179190, filed on 10 Jan 1994, now patented, Pat. No. US 5470880 which is a continuation of Ser. No. US 1993-89101, filed on 12 Jul 1993, now patented, Pat. No. US 5389677 which is a division of Ser. No. US 1993-8223, filed on 19 Jan 1993, now abandoned which is a continuation of Ser. No. US 1991-812858, filed on 23 Dec 1991, now abandoned which is a continuation of Ser. No. US 1990-469738, filed on 19 Jan 1990, now abandoned which is a continuation of Ser. No. US 1986-945680, filed on 23 Dec 1986, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Datlow, Philip I.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 1138
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The **composition** thus formulated contains 2% **hydroquinone**, 2% citric acid, 20% methyllactic acid, and has **pH** 3.6.

DETD Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 10% lactic acid, and has **pH** 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

DETD Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 5% **hydroquinone**, 8% glycolic acid, and has **pH** 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

DETD 2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 12% 2-methyl 2-hydroxypropanoic acid, and has **pH** 4.0. The composition solution is packaged in felt pens for

controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

DETD Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The **composition** thus prepared contains 5% **hydroquinone** and has **pH** 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

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L15 ANSWER 1 OF 14 USPATFULL

AB A method is provided for stabilizing alkylenebisdithiocarbamates, such as 1,2-ethylenebisdithiocarbamates, (EBDC) by mixing the EBDC with formaldehyde or formaldehyde releasing agents (donor) and a co-polymerization agent which forces the polymerization reaction of formaldehyde and ethylenethioureas toward completion to reduce and stabilize the content of and inhibit the formation of ethylenethiourea (ETU) in the EBDC. Paraformaldehyde as donor is preferably added in an amount of about 0.1 to 2 weight percent based upon the EBDC, together with a co-polymerization agent such as melamine or **hydroquinone** . The **stabilized** EBDC product contains aldehyde, co-polymerization agent, mono- and /or dimethylolethylenethioureas and polymerization products thereof, and less than about 0.015 weight percent ETU per se.

ACCESSION NUMBER: 91:44901 USPATFULL
TITLE: Enhanced reduction and inhibition of ETU content in alkylenebisdithiocarbamates
INVENTOR(S): Nouws, Jacobus A. M., Etten-leur, Netherlands
Kool, Pieter, Oostvoorne, Netherlands
Diepenhorst, Pieter C., Spijkenisse, Netherlands
PATENT ASSIGNEE(S): Pennwalt France S.A., Plaisir, France (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5021594		19910604	
APPLICATION INFO.:	US 1990-492526		19900312	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Prescott, Arthur C.
LEGAL REPRESENTATIVE: Panitch Schwarze Jacobs & Nadel
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
LINE COUNT: 395
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 2 OF 14 USPATFULL

AB Disclosed are anaerobic adhesive compositions which cure under anaerobic conditions, said compositions being comprised of at least one carboxylated cellulose ester such as carboxylated cellulose acetate butyrate or carboxylated cellulose acetate propionate, at least one acrylate monomer, and at least one **hydroquinone**-based **stabilizer**. The composition can optionally contain an accelerator.

ACCESSION NUMBER: 89:19216 USPATFULL
TITLE: Anaerobic adhesive compositions
INVENTOR(S): Sand, I. Daniel, Jonesborough, TN, United States
PATENT ASSIGNEE(S): Eastman Kodak Company, Rochester, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4812495		19890314	
APPLICATION INFO.:	US 1987-110158		19871019	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kight, John
ASSISTANT EXAMINER: Nutter, Nathan M.
LEGAL REPRESENTATIVE: Savitsky, Thomas R., Heath, Jr., William P.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
LINE COUNT: 1395
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 3 OF 14 USPATFULL

AB Stabilized vinyl halide compositions are provided by adding to said vinyl halide compositions an effective amount of a **stabilizer** having the substituted **hydroquinone** structure: ##STR1## wherein ##STR2## wherein p is 1 or 2 and

ACCESSION NUMBER:	89:3044 USPATFULL
TITLE:	Stabilized vinyl halide resins and compositions and articles made therefrom
INVENTOR(S):	Sharaby, Zaev, Cleveland Heights, OH, United States Vyvoda, Josef C., Avon Lake, OH, United States
PATENT ASSIGNEE(S):	The B. F. Goodrich Company, Akron, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4797443		19890110	
APPLICATION INFO.:	US 1985-728548		19850429	(6)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Hoke, Veronica P.			
LEGAL REPRESENTATIVE:	Powell, Joe A.			
NUMBER OF CLAIMS:	13			
EXEMPLARY CLAIM:	1			
LINE COUNT:	326			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 4 OF 14 USPATFULL

AB A skin bleaching skin preparation is disclosed. The preparation comprises hydroquinone, tertiary butyl **hydroquinone**, and optionally an additional **stabilizer**. The preparation can additionally contain a buffer to maintain the pH between about 3.5 and about 7.5. By maintaining this pH range in the presence of the tertiary butyl **hydroquinone stabilizer**, and optional additional **stabilizers**, the **hydroquinone** would not be oxidized, and thus the preparation would be characterized by an extended shelf life.

ACCESSION NUMBER:	88:82109 USPATFULL
TITLE:	Skin bleaching preparations
INVENTOR(S):	Filomeno, Vito G., Mt. Arlington, NJ, United States
PATENT ASSIGNEE(S):	Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4792443		19881220	
APPLICATION INFO.:	US 1987-55677		19870529	(7)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1985-811602, filed on 20 Dec 1985, now patented, Pat. No. US 4692261			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Willis, Prince E.			
LEGAL REPRESENTATIVE:	Jeanette, Henry C., Nath, Gary M.			
NUMBER OF CLAIMS:	8			
EXEMPLARY CLAIM:	1			
LINE COUNT:	750			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 5 OF 14 USPATFULL

AB A synthetic detergent bar is provided containing hydroquinone as a skin bleaching agent. The bar is maintained at a pH of between about 4 and 7 and includes a compressed mixture of a synthetic anionic detergent such as sodium cocoyl isethionate, sodium lauryl sulfoacetate and sodium methyl cocoyl tourate; **hydroquinone**, a **stabilizer**

for said **hydroquinone** such as tertiary butyl hydroquinone, water, a buffer which maintains the pH of the bar at about 4 to about 7 and excipients such as waxes, paraffin, dextrin and starches. Because of the maintenance of low pH and the presence of a **stabilizer**, **hydroquinone** is not oxidized and thus the bar is characterized by an extended shelf life.

ACCESSION NUMBER: 87:63452 USPATFULL
TITLE: Skin bleaching detergent bar
INVENTOR(S): Filomeno, Vito G., Mount Arlington, NJ, United States
PATENT ASSIGNEE(S): Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4692261		19870908	
APPLICATION INFO.:	US 1985-811602		19851220	(6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Willis, Prince E.
LEGAL REPRESENTATIVE: Scola, Jr., Daniel A., Jeanette, Henry C., Nath, Gary M.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1,2
LINE COUNT: 383
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 6 OF 14 USPATFULL
AB A water-in-oil explosives composition comprising water, liquid or liquefiable carbonaceous fuel and inorganic oxidizer salt, optionally with gassing agent and/or thickening agent, and containing 0.02 to 2% of a stabilizer selected from organo-sulphur compounds, organic compounds containing quaternary nitrogen, phenolic compounds and substituted derivatives thereof, dihydroxybenzenes, quinones, unsubstituted and substituted aryl diazo compounds, unsubstituted and substituted aryl amines and salts thereof, and unsubstituted and substituted quinolines. Preferred **stabilizers** include thioureo, **hydroquinone** , anthraquinone, 1-phenylazo-2-naphthol, 1-[(4'-o-tolylazo)-o-tolylazo]-2-naphthol, N-phenyl-.alpha.-naphthylamine, N-phenyl-.beta.-naphthylamine, the condensation products of 1,4 dichloroanthraquinone with p-toluidine and 2,2,4-trimethyl-1,2-dihydroquinolines.

ACCESSION NUMBER: 83:46403 USPATFULL
TITLE: Water-in-oil emulsion explosives and a method for the preparation of the same
INVENTOR(S): Bhattacharyya, Dhirendra N., Maharashtra, India
Seshan, Srinivasachari, Giridih, India
Campbell, John S., Maharastra, India
Sen, Soumendranath, Giridin, India
PATENT ASSIGNEE(S): Indian Explosives Limited, Calcutta, India (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4409044		19831011	
APPLICATION INFO.:	US 1982-442670		19821118	(6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lechert, Jr., Stephen J.
LEGAL REPRESENTATIVE: Cushman, Darby & Cushman
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 524
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 7 OF 14 USPATFULL
AB This invention provides a formulation comprising a thermosetting polyester, p-methylstyrene, a **hydroquinone stabilizer** , and 4,4'-thiobis-(3-methyl-6-t-butyl)-phenol.
ACCESSION NUMBER: 82:48507 USPATFULL
TITLE: Stabilized thermosetting polyester
INVENTOR(S): Murray, James G., East Brunswick, NJ, United States
PATENT ASSIGNEE(S): Mobil Oil Corporation, New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4352900		19821005	
APPLICATION INFO.:	US 1980-221609		19801231	(6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hoke, V. P.
LEGAL REPRESENTATIVE: Huggett, Charles A., Gilman, Michael G., Powers, Jr., James F.
NUMBER OF CLAIMS: 2
EXEMPLARY CLAIM: 1
LINE COUNT: 89
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 8 OF 14 USPATFULL
AB The present invention provides stable vinyl ester compositions exhibiting improved color stability comprising a vinyl ester resin prepared by esterifying an epoxy compound with an ethylenically unsaturated monocarboxylic acid and a **stabilizer** composition comprising **hydroquinone** and a sterically hindered phenol.
ACCESSION NUMBER: 81:65708 USPATFULL
TITLE: Vinyl ester resins having improved color
INVENTOR(S): Jackson, Roy J., Houston, TX, United States
PATENT ASSIGNEE(S): Shell Oil Company, Houston, TX, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4303579		19811201	
APPLICATION INFO.:	US 1980-166431		19800707	(6)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hoke, V. P.
LEGAL REPRESENTATIVE: Faringer, Norris E.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 407
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 9 OF 14 USPATFULL
AB A skin lightener based on **stabilized hydroquinone** in a moisturizing base which also contains a sunscreen agent.
ACCESSION NUMBER: 79:4487 USPATFULL
TITLE: Skin lightening composition
INVENTOR(S): Barnett, Gabriel, New York, NY, United States
Gershaw, Nathan, Commack, NY, United States
Mausner, Jack J., East Hills, NY, United States
PATENT ASSIGNEE(S): Helena Rubinstein, Inc., New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4136166		19790123	
APPLICATION INFO.:	US 1977-788440		19770418	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ore, Dale R.
LEGAL REPRESENTATIVE: Burgess, Ryan and Wayne
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
LINE COUNT: 184
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 10 OF 14 USPATFULL
AB **Hydroquinone** and alkylhydroquinone are thermal **stabilization** additives for normally solid polypyrrolidone at melt temperatures.
ACCESSION NUMBER: 78:39257 USPATFULL
TITLE: Extrusion stabilization of polypyrrolidone by hydroquinones
INVENTOR(S): Wedel, Carroll J., Walnut Creek, CA, United States
Parker, Phillip H., San Rafael, CA, United States
PATENT ASSIGNEE(S): Chevron Research Company, San Francisco, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4102861		19780725
APPLICATION INFO.:	US 1976-745891		19761129 (5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hoke, V. P.
LEGAL REPRESENTATIVE: Newell, Dix A., DeJonghe, Thomas G., Squires, Lawrence S.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 133
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 11 OF 14 USPATFULL
AB polyurethane foams are stabilized against scorching when a mixture of hydroquinone and a phosphite containing secondary antioxidant is present in a foam-forming mixture of an organic polyisocyanate with a polyether polyol in the presence of a reaction catalyst and a foaming agent. The proportion of hydroquinone to the phosphite is in the range of 10:1 to about 1:1. Especially advantageous results can be obtained by adding p,p'-dialkylphenylamines containing between 3 and 18 carbon atoms in the alkyl moiety to the above two stabilizers. When the amine is present the stabilizer mixture usually comprises between about 15 and 90% by weight of the amine and the rest of the **stabilizer** comprises the **hydroquinone** and the phosphite in the range relative to each other as given above. The proportion of the stabilizer mixture is usually between about 10 and about 50,000 parts per million parts of the polyether polyol. The stabilizer mixture is preferably mixed with the polyol before using the polyol in making urethane foams.
ACCESSION NUMBER: 78:12017 USPATFULL
TITLE: Polyurethane foam stabilized against scorch with a mixture of hydroquinone and a phosphite containing secondary antioxidant
INVENTOR(S): Baxter, Jr., William F., 225 Windmere Pl., Kingsport, TN, United States 37664
Douglas, Ted L., Rte. 10, Blakely Dr., Kingsport, TN, United States 37664
Irick, Gether, 424 Meadow La., Kingsport, TN, United States 37663

	NUMBER	KIND	DATE

PATENT INFORMATION: US 968002 19780307
APPLICATION INFO.: US 1977-771706 19770224 (5)
DOCUMENT TYPE: Defensive
FILE SEGMENT: Granted
NUMBER OF CLAIMS: 6
LINE COUNT: 16
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 12 OF 14 USPATFULL
AB The present invention is a method of treating mammals for alleviating inflammation by utilization of a non-steroid topical agent. The agent is ethyl linoleate [ethyl-cis,cis(9,12)-octadecadienoate] which may be combined in a preferred formulation with one or more antioxidants such as .alpha.-tocopherol, d,l-histidine, and tertiary butyl **hydroquinone**; a **stabilizer** such as Tween-80; and inert esters such as ethyl oleate, ethyl palmitate, and ethyl stearate. The agent is applied in a therapeutic dosage range of 0.2-0.8 mg/cm.sup.2 of body surface both internal and external, with a preferred dosage of 0.5 mg/cm.sup.2. This topical remedy for inflammation for internal and external body surfaces is utilized principally in a single dose but may be utilized in multiple doses are required due to low toxicity (60:1). Among the conditions with inflammatory responses amenable to treatment are ultraviolet ratiation, solar radiation, non-infectious conjunctivitis, hemorrhoids (acute), abrasions, ingrown finger or toenail (granulation), skin graft donor sites, vaginitis, poison ivy, psoriasis, herpes simplex (cold sores, aphthous ulcers), pruritis ani/cruri, chemical inflammation, and insect stings/bites.
ACCESSION NUMBER: 77:26930 USPATFULL
TITLE: Non-steroid topical agent for alleviating inflammation in mammals
INVENTOR(S): Jelenko, III, Carl, 2716 Wellington Drive, Augusta, GA, United States 30904

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4025645		19770524	
APPLICATION INFO.:	US 1976-652670		19760127	(5)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Friedman, Stanley J.
LEGAL REPRESENTATIVE: Roberts, Jr., John S.
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 408
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 13 OF 14 USPATFULL
AB Solutions of **hydroquinone** are **stabilized** against deterioration in color and odor with age by the addition to the solution of small amounts of citric acid. Up to about 1 percent citric acid by weight of the solution may be used, although it is preferred that this amount be between 0.005 percent and 0.05 percent.
ACCESSION NUMBER: 74:59270 USPATFULL
TITLE: STABILIZATION OF HYDROQUINONE SOLUTIONS WITH CITRIC ACID
INVENTOR(S): Weris, III, Arthur P., Kingsport, TN, United States
PATENT ASSIGNEE(S): Eastman Kodak Company, Rochester, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 3855150		19741217	
APPLICATION INFO.:	US 1973-344806		19730326	(5)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1970-46521, filed on 15 Jun

1970, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Padgett, Benjamin R.
ASSISTANT EXAMINER: Gluck, Irwin
LEGAL REPRESENTATIVE: Stevens, John F., Quillen, Jr., Cecil D.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 156
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 14 OF 14 USPATFULL

AB A liquid polysulfide polymer sealant composition for sealing glass to metal having greatly improved adhesion stability when exposed to ultraviolet radiation or sunlight transmitted through glass and greatly improved penetrometer cure and adhesion rate properties is obtained by use of **hydroquinone** and quinone ultraviolet radiation adhesion **stabilizers** and quaternary ammonium chloride curing and adhesion rate regulators.

ACCESSION NUMBER: 74:56349 USPATFULL
TITLE: LIQUID POLYSULFIDE POLYMER GLASS-TO-METAL SEALANT COMPOSITION
INVENTOR(S): Gallagher, John P., Milton Square, NJ, United States
Meyers, Robert M., Fairless Hills, PA, United States
Surg, Earl H., Trenton, NJ, United States
Willitts, Clark M., Levittown, PA, United States
PATENT ASSIGNEE(S): Thiokol Corporation, Bristol, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 3852214		19741203
APPLICATION INFO.:	US 1972-256737		19720525 (5)

RELATED APPLN. INFO.: Division of Ser. No. US 1970-76300, filed on 28 Sep 1970, now patented, Pat. No. US 3697472
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Padgett, Benjamin R.
ASSISTANT EXAMINER: Gluck, Irwin
LEGAL REPRESENTATIVE: Brennan, Thomas W.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 532
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 34 OF 35 USPATFULL

SUMM It has now been discovered that hydroxyacids and related compounds including those described or not described in our previous patents and additional compounds can substantially enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders or other afflictions. Cosmetic and pharmaceutical agents may include any chemical substances natural or synthetic, intended for topical application to the skin or its appendages in human and animals. Some examples of cosmetic and pharmaceutical agents include age spots and keratoses removing agents, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirants, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringents, softeners, emollient agents, coal tar, bath oils, sulfur, rinse conditioners, foot care agents, fungicides, hair growth promoters, hair removers, keratolytic agents, moisturizer agents, powder, shampoos, skin bleaches, skin protectants, soaps, cleansers, antiaging agents, sunscreen agents, wart removers, wet dressings, vitamins, tanning agents, topical antihistamin agents, hormones, vasodilators, **retinoids**, bronchial dilators, topical cardiovascular agents and other dermatologicals.

SUMM citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

SUMM Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the percutaneous penetration or the therapeutic efficacy of cosmetic and pharmaceutical agents. The cosmetic and pharmaceutical agents may include but not limited to: age spots and keratoses removing agents, vitamins, aloes, **retinoids**, sun screens; tanning, depigmenting and shampooing agents; antiperspirants, antiyeasts, antifungal, antibacterial and antiviral agents; topical bronchial dilators; topical cardiovascular agents; keratoses, age spots and wrinkles removal agents, hair growth promoting agents and other dermatological agents.

DETD Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The **composition** thus formulated contains **hydroquinone**, 2% citric acid, 20% methyllactic acid, and has **pH** 3.6.

DETD Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 10% lactic acid, and has **pH** 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

DETD Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained.

The **composition** thus formulated contains 5% **hydroquinone**, 8% glycolic acid, and has **pH** 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

DETD 2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 12% 2-methyl 2-hydroxypropanoic acid, and has **pH** 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

DETD Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The **composition** thus prepared contains 5% **hydroquinone** and has **pH** 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

DETD Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, gulonolactone, mannonolactone, citramalic acid.

ACCESSION NUMBER: 95:50194 USPATFULL

TITLE: Method of using 2-hydroxypropanoic acid (lactic acid) for the treatment of wrinkles

INVENTOR(S): Yu, Ruey J., 4 Lindenwold Ave., Ambler, PA, United States 19002
Van Scott, Eugene J., 3 Hidden La., Abington, PA, United States 19001

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5422370		19950606
APPLICATION INFO.:	US 1994-179189		19940110 (8)

DISCLAIMER DATE: 20090225

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-89101, filed on 12 Jul 1993 which is a division of Ser. No. US 1993-8223, filed on 22 Jan 1993 which is a continuation of Ser. No. US 1991-812858, filed on 23 Dec 1991, now abandoned which is a continuation of Ser. No. US 1990-469738, filed on 19 Jan 1990, now abandoned which is a continuation of Ser. No. US 1986-945680, filed on 23 Dec 1986, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Shah, Mukund J.

ASSISTANT EXAMINER: Datlow, Philip I.

LEGAL REPRESENTATIVE: Foley & Lardner

NUMBER OF CLAIMS: 11

EXEMPLARY CLAIM: 1

LINE COUNT: 1116

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 35 OF 35 USPATFULL

AB Composition and method for enhancing therapeutic effects of topically applied agents are disclosed. The cosmetic or therapeutic composition may include one or more of cosmetic or pharmaceutical agents present in

a total amount of from 0.01 to 40 percent and one or more of hydroxycarboxylic acids or related compounds present in a total amount of from 0.01 to 99 percent by weight of the total composition. The cosmetic and pharmaceutical agents may include but not limited to age spots, wrinkles and keratoses removing agents; vitamins; aloes; sun screens; tanning, depigmenting and shampooing agents; antiyeasts; antifungal, antibacterial and antiviral agents; topical bronchial dilators and topical cardiovascular agents; hormonal agents; vasodilators; **retinoids** and other dermatological agents. The hydroxycarboxylic acids and related compounds include organic alpha and beta hydroxycarboxylic acids, alpha and beta ketocarboxylic acids and salts thereof. Topical application of the cosmetic or therapeutic composition has been found to achieve a substantial increase in cosmetic or therapeutic effect of the active ingredient in humans and domesticated animals.

SUMM It has now been discovered that hydroxyacids and related compounds including those described or not described in our previous patents and additional compounds can substantially enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders or other afflictions. Cosmetic and pharmaceutical agents may include any chemical substances natural or synthetic, intended for topical application to the skin or its appendages in human and animals. Some examples of cosmetic and pharmaceutical agents include age spots and keratoses removing agents, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirants, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringents, softeners, emollient agents, coal tar, bath oils, sulfur, rinse conditioners, foot care agents, fungicides, hair growth promoters, hair removers, keratolytic agents, moisturizer agents, powder, shampoos, skin bleaches, skin protectants, soaps, cleansers, antiaging agents, sunscreen agents, wart removers, wet dressings, vitamins, tanning agents, topical antihistamin agents, hormones, vasodilators, **retinoids**, bronchial dilators, topical cardiovascular agents and other dermatologicals.

SUMM citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

SUMM Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the percutaneous penetration or the therapeutic efficacy of cosmetic and pharmaceutical agents. The cosmetic and pharmaceutical agents may include but not limited to: age spots and keratoses removing agents, vitamins, aloes, **retinoids**, sun screens; tanning, depigmenting and shampooing agents; antiperspirants, antiyeasts, antifungal, antibacterial and antiviral agents; topical bronchial dilators; topical cardiovascular agents; keratoses, age spots and wrinkles removal agents, hair growth promoting agents and other dermatological agents.

DETD Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The **composition** thus formulated contains 2% **hydroquinone**,

2% citric acid, 20% methyllactic acid, and has **pH** 3.6.

DETD Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 10% lactic acid, and has **pH** 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

DETD Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 5% **hydroquinone**, 8% glycolic acid, and has **pH** 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

DETD 2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 12% 2-methyl 2-hydroxypropanoic acid, and has **pH** 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

DETD Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The **composition** thus prepared contains 5% **hydroquinone** and has **pH** 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

DETD Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, gulonolactone, mannonolactone, citramalic acid.

ACCESSION NUMBER: 95:13910 USPATFULL

TITLE: Method of treating wrinkles using glycalic acid

INVENTOR(S): Yu, Ruey J., 4 Lindenwold Ave., Ambler, PA, United States 19002
Van Scott, Eugene J., 3 Hidden La., Abington, PA, United States 19001

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5389677		19950214
APPLICATION INFO.:	US 1993-89101		19930712 (8)

DISCLAIMER DATE: 20090225

RELATED APPLN. INFO.: Division of Ser. No. US 1993-8223, filed on 22 Jan 1993 which is a continuation of Ser. No. US 1991-812858, filed on 23 Dec 1991, now abandoned which is a continuation of Ser. No. US 1990-469738, filed on 19 Jan 1990, now abandoned which is a continuation of Ser. No. US 1986-945680, filed on 23 Dec 1986, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Shah, Mukund J.

ASSISTANT EXAMINER: Datlow, Philip I.

LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 1113
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 17 OF 35 USPATFULL

SUMM It has now been discovered that hydroxyacids and related compounds including those described or not described in our previous patents and additional compounds can substantially enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders or other afflictions. Cosmetic and pharmaceutical agents may include any chemical substances natural or synthetic, intended for topical application to the skin or its appendages in human and animals. Some examples of cosmetic and pharmaceutical agents include age spots and keratoses removing agents, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirants, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringents, softeners, emollient agents, coal tar, bath oils, sulfur, rinse conditioners, foot care agents, fungicides, hair growth promoters, hair removers, keratolytic agents, moisturizer agents, powder, shampoos, skin bleaches, skin protectants, soaps, cleansers, antiaging agents, sunscreen agents, wart removers, wet dressings, vitamins, tanning agents, topical antihistamin agents, hormones, vasodilators, **retinoids**, bronchial dilators, topical cardiovascular agents and other dermatologicals.

SUMM citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

SUMM Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the percutaneous penetration or the therapeutic efficacy of cosmetic and pharmaceutical agents. The cosmetic and pharmaceutical agents may include but not limited to: age spots and keratoses removing agents, vitamins, aloes, **retinoids**, sun screens; tanning, depigmenting and shampooing agents; antiperspirants, antiyeasts, antifungal, antibacterial and antiviral agents; topical bronchial dilators; topical cardiovascular agents; keratoses, age spots and wrinkles removal agents, hair growth promoting agents and other dermatological agents.

DETD Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The **composition** thus formulated contains 2% **hydroquinone**, 2% citric acid, 20% methyllactic acid, and has **pH** 3.6.

DETD Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 10% lactic acid, and has **pH** 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

DETD Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 5%

hydroquinone, 8% glycolic acid, and has **pH** 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

DETD 2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 12% 2-methyl 2-hydroxypropanoic acid, and has **pH** 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

DETD Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The **composition** thus prepared contains 5% **hydroquinone** and has **pH** 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

DETD Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, gulonolactone, mannonolactone, citramalic acid.

ACCESSION NUMBER: 96:109012 USPATFULL
TITLE: Method of treating wrinkles using isocitric acid
INVENTOR(S): Yu, Ruey J., Ambler, PA, United States
Van Scott, Eugene J., Abington, PA, United States
PATENT ASSIGNEE(S): Tristrata Technology, Inc., Wilmington, DE, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5578644		19961126
APPLICATION INFO.:	US 1995-471518		19950606 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-179190, filed on 10 Jan 1994, now patented, Pat. No. US 5470880 which is a continuation of Ser. No. US 1993-89101, filed on 12 Jul 1993, now patented, Pat. No. US 5389677 which is a division of Ser. No. US 1993-8223, filed on 22 Jan 1993, now abandoned which is a continuation of Ser. No. US 1991-812858, filed on 23 Dec 1991, now abandoned which is a continuation of Ser. No. US 1990-469738, filed on 19 Jan 1990, now abandoned which is a continuation of Ser. No. US 1986-945680, filed on 23 Dec 1986, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Datlow, Philip I.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 1123
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 18 OF 35 USPATFULL

SUMM It has now been discovered that hydroxyacids and related compounds including those described or not described in our previous patents and additional compounds can substantially enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic

conditions, dermatologic disorders or other afflictions. Cosmetic and pharmaceutical agents may include any chemical substances natural or synthetic, intended for topical application to the skin or its appendages in human and animals. Some examples of cosmetic and pharmaceutical agents include age spots and keratoses removing agents, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirants, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringents, softeners, emollient agents, coal tar, bath oils, sulfur, rinse conditioners, foot care agents, fungicides, hair growth promoters, hair removers, keratolytic agents, moisturizer agents, powder, shampoos, skin bleaches, skin protectants, soaps, cleansers, antiaging agents, sunscreen agents, wart removers, wet dressings, vitamins, tanning agents, topical antihistamin agents, hormones, vasodilators, **retinoids**, bronchial dilators, topical cardiovascular agents and other dermatologicals.

SUMM citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

SUMM Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the percutaneous penetration or the therapeutic efficacy of cosmetic and pharmaceutical agents. The cosmetic and pharmaceutical agents may include but not limited to: age.spots and keratoses removing agents, vitamins, aloes, **retinoids**, sun screens; tanning, depigmenting and shampooing agents; antiperspirants, antiyeasts, antifungal, antibacterial and antiviral agents; topical bronchial dilators; topical cardiovascular agents; keratoses, age spots and wrinkles removal agents, hair growth promoting agents and other dermatological agents.

DETD Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The **composition** thus formulated contains 2% **hydroquinone**, 2% citric acid, 20% methyllactic acid, and has **pH** 3.6.

DETD Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 10% lactic acid, and has **pH** 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

DETD Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 5% **hydroquinone**, 8% glycolic acid, and has **pH** 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin

lesions.

DETD 2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 12% 2-methyl 2-hydroxypropanoic acid, and has **pH** 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

DETD Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The **composition** thus prepared contains 5% **hydroquinone** and has **pH** 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

DETD Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, gulonolactone, mannonolactone, citramalic acid.

ACCESSION NUMBER: 96:104030 USPATFULL

TITLE: Method of treating wrinkles using gluconic acid or gluconolactone

INVENTOR(S): Yu, Ruey J., Ambler, PA, United States
Van Scott, Eugene J., Abington, PA, United States

PATENT ASSIGNEE(S): Tristrata Technology, Inc., Wilmington, DE, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5574067		19961112
APPLICATION INFO.:	US 1995-467001		19950606 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-179190, filed on 10 Jan 1994, now patented, Pat. No. US 5470880 which is a continuation of Ser. No. US 1993-89101, filed on 12 Jul 1993, now patented, Pat. No. US 5389677 which is a division of Ser. No. US 1993-8223, filed on 22 Jan 1993, now abandoned which is a continuation of Ser. No. US 1991-812858, filed on 23 Dec 1991, now abandoned which is a continuation of Ser. No. US 1990-469738, filed on 9 Jan 1990, now abandoned which is a continuation of Ser. No. US 1986-945680, filed on 23 Dec 1986, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Datlow, Philip I.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 1118
CAS INDEXING IS AVAILABLE FOR THIS

L21 ANSWER 3 OF 35 USPATFULL

AB Composition and method for enhancing therapeutic effects of topically applied agents are disclosed. The cosmetic or therapeutic composition may include one or more of cosmetic or pharmaceutical agents present in a total amount of from 0.01 to 40 percent and one or more of hydroxycarboxylic acids or related compounds present in a total amount of from 0.01 to 99 percent by weight of the total composition. The cosmetic and pharmaceutical agents may include but not limited to age spots, wrinkles and keratoses removing agents; vitamins; aloes; sun screens; tanning, depigmenting and shampooing agents; antiyeasts; antifungal, antibacterial and antiviral agents; topical bronchial dilators and topical cardiovascular agents; hormonal agents; vasodilators; **retinoids** and other dermatological agents. The hydroxycarboxylic acids and related compounds include organic alpha and beta hydroxycarboxylic acids, alpha and beta ketocarboxylic acids and salts thereof. Topical application of the cosmetic or therapeutic composition has been found to achieve a substantial increase in cosmetic or therapeutic effect of the active ingredient in humans and domesticated animals.

SUMM It has now been discovered that hydroxyacids and related compounds including those described or not described in our previous patents and additional compounds can substantially enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders or other afflictions. Cosmetic and pharmaceutical agents may include any chemical substances natural or synthetic, intended for topical application to the skin or its appendages in human and animals. Some examples of cosmetic and pharmaceutical agents include age spots and keratoses removing agents, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirants, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringents, softeners, emollient agents, coal tar, bath oils, sulfur, rinse conditioners, foot care agents, fungicides, hair growth promoters, hair removers, keratolytic agents, moisturizer agents, powder, shampoos, skin bleaches, skin protectants, soaps, cleansers, antiaging agents, sunscreen agents, wart removers, wet dressings, vitamins, tanning agents, topical antihistamin agents, hormones, vasodilators, **retinoids**, bronchial dilators, topical cardiovascular agents and other dermatologicals.

SUMM citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galacturonic-acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

SUMM Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the percutaneous penetration or the therapeutic efficacy of cosmetic and pharmaceutical agents. The cosmetic and pharmaceutical agents may include but not limited to: age spots and keratoses removing agents, vitamins, aloes, **retinoids**, sun screens; tanning, depigmenting and shampooing agents; antiperspirants, antiyeasts, antifungal, antibacterial and antiviral agents; topical bronchial dilators; topical cardiovascular agents; keratoses, age spots and wrinkles removal agents, hair growth promoting agents and other dermatological agents.

DETD Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The **composition** thus formulated contains 2% **hydroquinone**, 2% citric acid, 20% methyllactic acid, and has **pH** 3.6.

DETD Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 10% lactic acid, and has **pH** 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

DETD Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 5% **hydroquinone**, 8% glycolic acid, and has **pH** 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

DETD A therapeutic composition containing hydroquinone and 2-methyl 2-hydroxypropanoic acid in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows. 2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 12% 2-methyl 2-hydroxypropanoic acid, and has **pH** 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

DETD Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The **composition** thus prepared contains 5% **hydroquinone** and has **pH** 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

DETD Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, gulonolactone, mannonolactone, citramalic acid.

CLM What is claimed is:

7. The composition of claim 6, wherein the hydroxyacid is selected from the group consisting of citric acid, isocitric acid, citramalic acid, agaricic acid, quicnic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2,2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid and 4-hydroxy-3-pentenoic acid.

15. The method of claim 14, wherein the hydroxyacid is selected from the group consisting of citric acid, isocitric acid, citramalic acid,

agaricic acid, quicnic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2,2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid and 4-hydroxy-3-pentenoic acid.

23. The method of claim 22, wherein the hydroxyacid is selected from the group consisting of citric acid, isocitric acid, citramalic acid, agaricic acid, quicnic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2,2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid and 4-hydroxy-3-pentenoic acid.

ACCESSION NUMBER: 1999:121427 USPATFULL
TITLE: Pharmaceutical compositions containing hydroxycarboxylic acids and/or ketocarboxylic acids and methods of using same
INVENTOR(S): Yu, Ruey J., Ambler, PA, United States
Van Scott, Eugene J., Rydal, PA, United States
PATENT ASSIGNEE(S): Tristrata Technology, Inc., Wilmington, DE, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5962526		19991005
APPLICATION INFO.:	US 1997-926030		19970909 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-487684, filed on 7 Jun 1995, now patented, Pat. No. US 5691378 which is a continuation of Ser. No. US 1994-179190, filed on 10 Jan 1994, now patented, Pat. No. US 5470880 which is a continuation of Ser. No. US 1993-89101, filed on 12 Jul 1993, now patented, Pat. No. US 5389677 which is a continuation of Ser. No. US 1993-8223, filed on 22 Jan 1993, now patented, Pat. No. US 5665776 which is a continuation of Ser. No. US 1991-812858, filed on 23 Dec 1991, now abandoned which is a continuation of Ser. No. US 1990-469738, filed on 19 Jan 1990, now abandoned which is a continuation of Ser. No. US 1986-945680, filed on 23 Dec 1986, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Dees, Jose' G.
ASSISTANT EXAMINER: Williamson, Michael A.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 1327
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 4 OF 35 USPATFULL
AB Composition and method for enhancing therapeutic effects of topically applied agents are disclosed. The cosmetic or therapeutic composition may include one or more of cosmetic or pharmaceutical agents present in a total amount of from 0.01 to 40 percent and one or more of hydroxycarboxylic acids or related compounds present in a total amount of from 0.01 to 99 percent by weight of the total composition. The

cosmetic and pharmaceutical agents may include but not limited to age spots, wrinkles and keratoses removing agents; vitamins; aloes; sun screens; tanning, depigmenting and shampooing agents; antiyeasts; antifungal, antibacterial and antiviral agents; topical bronchial dilators and topical cardiovascular agents; hormonal agents; vasodilators; **retinoids** and other dermatological agents. The hydroxycarboxylic acids and related compounds include organic alpha and beta hydroxycarboxylic acids, alpha and beta ketocarboxylic acids and salts thereof. Topical application of the cosmetic or therapeutic composition has been found to achieve a substantial increase in cosmetic or therapeutic effect of the active ingredient in humans and domesticated animals.

SUMM It has now been discovered that hydroxyacids and related compounds including those described or not described in our previous patents and additional compounds can substantially enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders or other afflictions. Cosmetic and pharmaceutical agents may include any chemical substances natural or synthetic, intended for topical application to the skin or its appendages in human and animals. Some examples of cosmetic and pharmaceutical agents include age spots and keratoses removing agents, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirants, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatic agents, antiseborrheic agents, astringents, softeners, emollient agents, coal tar, bath oils, sulfur, rinse conditioners, foot care agents, fungicides, hair growth promoters, hair removers, keratolytic agents, moisturizer agents, powder, shampoos, skin bleaches, skin protectants, soaps, cleansers, antiaging agents, sunscreen agents, wart removers, wet dressings, vitamins, tanning agents, topical antihistamin agents, hormones, vasodilators, **retinoids**, bronchial dilators, topical cardiovascular agents and other dermatologicals.

SUMM citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galacturonic-acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

SUMM Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the percutaneous penetration or the therapeutic efficacy of cosmetic and pharmaceutical agents. The cosmetic and pharmaceutical agents may include but not limited to: age spots and keratoses removing agents, vitamins, aloes, **retinoids**, sun screens; tanning, depigmenting and shampooing agents; antiperspirants, antiyeasts, antifungal, antibacterial and antiviral agents; topical bronchial dilators; topical cardiovascular agents; keratoses, age spots and wrinkles removal agents, hair growth promoting agents and other dermatological agents.

DETD Alpha hydroxyisobutyric acid (Methyllactic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The **composition** thus formulated contains 2% **hydroquinone**, 2% citric acid, 20% methyllactic acid, and has **pH** 3.6.

DETD Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and

propylene glycol 6 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 10% lactic acid, and has **pH** 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

DETD Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 5% **hydroquinone**, 8% glycolic acid, and has **pH** 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

DETD 2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The **composition** thus formulated contains 4% **hydroquinone**, 12% 2-methyl 2-hydroxypropanoic acid, and has **pH** 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

DETD Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The **composition** thus prepared contains 5% **hydroquinone** and has **pH** 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

DETD Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, **ascorbic** acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, gulonolactone, mannonolactone, citramalic acid.

ACCESSION NUMBER: 1999:40471 USPATFULL

TITLE: Method of using beta hydroxy acids for treating wrinkles

INVENTOR(S): Yu, Ruey J., Ambler, PA, United States
Van Scott, Eugene J., Rydal, PA, United States

PATENT ASSIGNEE(S): Tristrata Technology, Inc., Wilmington, DE, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5889054		19990330
APPLICATION INFO.:	US 1997-925063		19970908 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-487684, filed on 7 Jun 1995, now patented, Pat. No. US 5691378 which is a continuation of Ser. No. US 1994-179190, filed on 10 Jan 1994, now patented, Pat. No. US 5470880 which is a continuation of Ser. No. US 1993-89101, filed on 12 Jul 1993, now patented, Pat. No. US 5389677 which is a continuation of Ser. No. US 1993-8223, filed on 22 Jan 1993, now patented, Pat. No. US 5665776 which is a continuation of Ser. No. US 1991-812858, filed on 23 Dec 1991, now abandoned which is a continuation of Ser. No. US 1990-469738, filed on 19 Jan 1990, now abandoned which is a continuation of Ser. No. US 1986-945680, filed on 23 Dec 1986, now abandoned

DOCUMENT TYPE:	Utility
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PRIMARY EXAMINER:	Dees, Jose' G.
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LEGAL REPRESENTATIVE:	Foley & Lardner
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
LINE COUNT:	1200

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L72 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 2003:132326 CAPLUS
DN 138:158532
TI Hair **preparations** containing henna powder or henna extracts and antioxidants
IN Togane, Atsumu; Maruyama, Takamasa
PA Chuo Airzole Kagaku K. K., Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K007-06
ICS A61K007-075; A61K007-08; A61K007-11; A61K007-13
CC 62-3 (Essential Oils and Cosmetics)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 2003048818	A2	20030221	JP 2001-266508	20010731
PRAI JP 2001-266508		20010731		

AB The **prepns**., which are prevented from deterioration of henna due to condensation of lawsone,contain henna powder with diam. .ltoreq.2 mm or henna exts., antioxidants, hair dyes, and optionally .gtoreq.1 selected from oily components, polymer components, surfactants, solvents, powders, thickeners, gelling agents, stabilizers, acids and alkalies, **pH** controllers, ion sequestering agents, dyes and pigments, antiseptics, lustering agents, moisturizers, nutrients, anti-inflammatory agents, cooling agents, perfumes, and H2O. A **compn**. contg. henna leaf alc. ext., hydroquinone, p-C6H4(NH2)2, 2-nitro-p-phenylenediamine, NH3 water, polyoxyethylene glyceryl monooleate, polyoxyethylene hydrogenated castor oil, white petrolatum, and H2O was mixed with H2O2 soln. just before use and applied to gray hair. The hair was uniformly dyed and glossy and smooth.
ST henna hair dye lawsone deterioration prevention antioxidant; ascorbate lawsone deterioration prevention henna hair dye
IT Hair **preparations**
(dyes; hair **prepns**. contg. henna powder or henna exts., antioxidants to prevent deterioration of lawsone, and hair dyes)
IT Antioxidants
Hair **preparations**
Lawsonia inermis
(hair **prepns**. contg. henna powder or henna exts., antioxidants to prevent deterioration of lawsone, and hair dyes)
IT 83-72-7, Lawsone
RL: COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(hair **prepns**. contg. henna powder or henna exts., antioxidants to prevent deterioration of lawsone, and hair dyes)
IT 87-66-1, Pyrogallol **123-31-9**, Hydroquinone, biological studies
7757-83-7, Sodium sulfite 25395-66-8, Ascorbyl stearate
108910-78-7, **Magnesium ascorbate phosphate**
RL: COS (Cosmetic use); MOA (Modifier or additive use); BIOL (Biological study); USES (Uses)
(hair **prepns**. contg. henna powder or henna exts., antioxidants to prevent deterioration of lawsone, and hair dyes)

L72 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 2002:905838 CAPLUS
DN 137:389183
TI **Compositions** for the treatment of pigmentation disorders and methods for their manufacture
IN Wortzman, Mitchell S.; Gordon, Philip J.; Gans, Eugene H.; Patel, Bhiku G.
PA Medicis Pharmaceutical Corp., USA
SO PCT Int. Appl., 25 pp.

CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-02
ICS A61K031-34; A61K031-20; A61K033-04
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002094251	A1	20021128	WO 2002-US15548	20020516
US 2003053968	A1	20030320	US 2001-864083	20010523

PI W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-864083 A 20010523

AB The present invention addresses the problem of excessive discoloration in hydroquinone **compns**. of a neutral **pH**. Antioxidants in the hydroquinone phase and inorg. or amino acyl cationic salts of acidic ascorbyl esters, preferably sodium metabisulfite and **magnesium ascorbyl phosphate** resp., are effective in stabilizing such hydroquinone **compns**., which are used in treatment of pigmentation disorders. Protected retinoid may be added to these **compns**. for addnl. skin benefit effects.

ST skin pigmentation disorder hydroquinone antioxidant formulation

IT Drug delivery systems
(carriers; hydroquinone **compns**. for the treatment of pigmentation disorders and methods for their manuf.)

IT **pH**
(hydroquinone **compns**. for the treatment of pigmentation disorders and methods for their manuf.)

IT Retinoids
Sulfites
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(hydroquinone **compns**. for the treatment of pigmentation disorders and methods for their manuf.)

IT Skin, disease
(pigmentation; hydroquinone **compns**. for the treatment of pigmentation disorders and methods for their manuf.)

IT Drug delivery systems
(topical; hydroquinone **compns**. for the treatment of pigmentation disorders and methods for their manuf.)

IT Antioxidants
(water-sol.; hydroquinone **compns**. for the treatment of pigmentation disorders and methods for their manuf.)

IT 50-81-7D, Ascorbic acid, esters 68-26-8, Retinol 116-31-4, Retinal **123-31-9**, Hydroquinone, biological studies 302-79-4, Retinoic acid 4759-48-2, Isotretinoin 7681-57-4, Sodium metabisulfite 113170-55-1 220644-17-7
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(hydroquinone **compns**. for the treatment of pigmentation disorders and methods for their manuf.)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Duffy; US 5703122 A 1997 CAPLUS

(2) Kawato; US 6139854 A 2000 CAPLUS
(3) Lorenzi; US 6217889 B1 2001 CAPLUS

=> d 3-10 hit, ibib

L72 ANSWER 3 OF 10 USPATFULL
TI **Compositions** for the treatment of pigmentation disorders and methods for their manufacture
AB The present invention addresses the problem of excessive discoloration in hydroquinone **compositions** of a neutral **pH**. Antioxidants in the hydroquinone phase and inorganic or amino acyl cationic salts of acidic ascorbyl esters, preferably sodium metabisulfite and **magnesium ascorbyl phosphate** respectively, are effective in stabilizing such hydroquinone **compositions**, which are used in treatment of pigmentation disorders. Protected retinoid may be added to these **compositions** for additional skin benefit effects.
SUMM [0001] This invention relates to methods and **compositions** for the treatment of pigmentation disorders, including hyperpigmentation and vitiligo.

SUMM [0003] In the United States, the most commonly used treatment for hyperpigmentation is 1,4-benzenediol, which is known as hydroquinone. Treatment with hydroquinone interferes with the action of tyrosinase, which is an enzyme used in the synthesis of melanin, and **compositions** are sold across the counter at about 2% hydroquinone and by prescription at higher concentrations.

SUMM [0004] Hydroquinone **compositions** are effective but have some undesirable side effects. These can be burning, redness, sensitization and irritation in some patients.

SUMM [0005] Additionally, the hydroquinone **compositions** frequently discolor over time and turn from a whitish color to a brown or even black. Without being limited to the mechanism of this discoloration, it is believed that the discoloration may be caused at least in part by oxidation of the hydroquinone. Discoloration of hydroquinone **compositions** may be accelerated by repeated exposure to oxygen or exposing the **compositions** to high temperatures, which may be found inside a car or delivery vehicle on a hot sunny day.

SUMM [0006] The natural **pH** for conventional hydroquinone **compositions** is acidic, generally less than about 4 even though this is harsh to the skin and to other components of the product. This range of **pH** has been preferred for hydroquinone **compositions**, because it has been believed that the hydroquinone is less likely to excessively discolor under acid conditions. Variations in **pH** have proven to result in excessive discoloration ranging from brownish to black. The present invention combats this problem, with hydroquinone **compositions** in the neutral **pH** range, preferably a **pH** of from about 5.5 to about 8.0, more preferably a **pH** of from about 5.5 to about 7.5, and most preferably at a **pH** of from about 6.0 to about 7.5.

SUMM [0007] Some hydroquinone **compositions** include antioxidants, such as ascorbyl palmitate. Other antioxidants, for example cationic salts of acidic ascorbyl esters, most preferably **magnesium ascorbyl phosphate**, aminopropyl ascorbyl phosphate, and sodium ascorbyl phosphate, have not been utilized in combination with hydroquinone in view of the acidic **pH**, generally from about 3.4 to about 3.5, and the recommended **pH** range for **magnesium ascorbyl phosphate** is about 7.0 to 8.5. However, hydroquinone discolors at the **pH** range of 7.0 to

8.5. Thus, while cationic salts of acidic ascorbyl esters, preferably **magnesium ascorbyl phosphate** and aminopropyl ascorbyl phosphate, have beneficial antioxidant effects on the skin, the combination with hydroquinone in the invention results in a compatible and stable **composition**.

SUMM [0008] Antioxidants, preferably sulfites, including but not limited to sulfites, bisulfites, metabisulfites, their salts, and their derivatives, most preferably sodium metabisulfite, have been used to stabilize certain **compositions**, which have included hydroquinone. Since hydroquinone has a tendency to discolor through oxidation, these antioxidants are used because they have greater tendencies to oxidize than hydroquinone. Sodium metabisulfite has the added advantage that it does not discolor by oxidation. In hydroquinone and sodium metabisulfite **compositions**, it is believed that the sodium metabisulfite oxidizes first and delays the start of any oxidation of the hydroquinone, so that excessive discoloration is delayed or totally avoided. However, these hydroquinone-containing **compositions** were in the acidic **pH** range and did not contain cationic salts of acidic ascorbyl esters, such as **magnesium ascorbyl phosphate**.

SUMM [0009] While patients suffer from pigmentation disorders, they may also suffer from other skin disorders and signs of aging, including but not limited to rough skin texture, mottled pigmentation, sallow complexion, lines and wrinkles. Retinoid **compositions**, in particular retinoic acid, retinal, and their derivatives, isomers and analogs (such as adapalene, tazarotene and isotretoin) are known to be effective in improving rough skin texture, mottled pigmentation, sallow complexion, lines and wrinkles.

SUMM [0010] It would be desirable to combine the pigmentation disorder treatment with this skin benefit ingredient in one **composition** . However, a problem with a formulation containing both retinoids and hydroquinone has been their incompatible **pH** ranges. Thus, merely adding one retinoid to a hydroquinone **composition** would result in instability and/or discoloration, and adding hydroquinone to a retinoid product would have a similar result.

SUMM [0011] This invention addresses the problem of formulating a pigmentation disorder treatment **composition** with hydroquinone without an excessive discoloration of the **composition** in the **pH** range of about 7.0. We have discovered that a hydroquinone **composition** (with about 1 to about 12% hydroquinone, preferably with about 2% to about 10%, more preferably with about 2% to about 8%, more preferably with about 2% to about 4%, most preferably with about 3% to about 4% hydroquinone) with preferably a **pH** of from about 5.5 to about 8.0, more preferably a **pH** of from about 5.5 to about 7.5, and most preferably at a **pH** of from about 6.0 to about 7.5, can include cationic salts of acidic ascorbyl esters, preferably sodium ascorbyl phosphate, more preferably aminopropyl ascorbyl phosphate, most preferably **magnesium ascorbyl phosphate** as an antioxidant and the color destabilization problems are appreciably less as compared to hydroquinone **compositions** without such a cationic salt of acidic ascorbyl esters in the neutral **pH** range: preferably a **pH** of from about 5.5 to about 8.0, more preferably a **pH** of from about 5.5 to about 7.5, and most preferably at a **pH** of from about 6.0 to about 7.5.

SUMM [0012] Additionally, a water-soluble antioxidant, preferably a sulfite, including but not limited to sulfites, bisulfites, metabisulfites, their salts and their derivatives, most preferably sodium metabisulfite, may be helpful in stabilizing the hydroquinone **composition**. Most

preferably, when both a water-soluble antioxidant, preferably sulfite, including but not limited to sulfites, bisulfites, metabisulfites, their salts and their derivatives, most preferably sodium metabisulfite, and a cationic salt of acidic ascorbyl esters, most preferably **magnesium ascorbyl phosphate**, are present, the color of the hydroquinone **composition** is stabilized in the neutral **pH** range, preferably for greater than about six months, more preferably for greater than about twelve months and most preferably for greater than about eighteen months.

SUMM [0013] Since the neutral **pH** of the hydroquinone **composition** with sodium metabisulfite and **magnesium ascorbyl phosphate** is preferably from about 5.5 to about 8.0, more preferably a **pH** of from about 5.5 to about 7.5, and most preferably at a **pH** of from about 6.0 to about 7.5, the **pH** is acceptable for also including retinoids in the **composition**.

SUMM [0014] Unfortunately, retinoids, in particular retinoic acid, retinal, and their derivatives, isomers and analogs (such as adapalene, tazarotene and isotretoin) also have discoloration problems due to oxidation. Forms of retinoids have been developed wherein the retinoid is protected by a protective system. The protective system can be an entrapment system, a single or multi-laminar system, such as by the formation of vesicles such as a liposome or by utilizing wax, paraffin, silicone, polyethylene, or any material or system which protects the retinoid from oxidation. The preferred protected retinoid is in the form of small beads or vesicles which are of a form that can be adjusted to be incorporated into varied topical **compositions**.

SUMM [0015] Retinoids, in particular retinoic acid, retinal, and their derivatives, isomers and analogs (such as adapalene, tazarotene and isotretoin), which are protected have been shown to also be color stable in hydroquinone, **magnesium ascorbyl phosphate** and sodium metabisulfite **composition** at about a neutral **pH**, preferably from about 5.5 to about 8.0, more preferably from about 5.5 to about 7.5, and most preferably from about 6.0 to about 7.5. Retinoids are included in the invention from about 0.01 to about 5%, preferably from about 0.025% to about 2.0%, more preferably from about 0.05% to about 1%, and most preferably from about 0.025% to about 0.5%.

SUMM [0016] A further embodiment of the invention includes a method for stabilizing a hydroquinone **composition** (with about 1% to about 12% hydroquinone, preferably about 2% to about 10%, more preferably about 2% to about 8%, and most preferably about 3% to about 4%) with a neutral **pH** of from about 5.5 to about 8.0, more preferably a **pH** of from about 5.5 to about 7.5, and most preferably at a **pH** of from about 6.0 to about 7.5, by adding a water-soluble antioxidant, preferably sulfite, including but not limited to sulfites, bisulfites, metabisulfites, their salts and their derivatives, most preferably sodium metabisulfite, and a cationic salt of acidic ascorbyl esters, preferably sodium ascorbyl phosphate, more preferably aminopropyl ascorbyl phosphate, most preferably **magnesium ascorbyl phosphate**. Protected retinoid, with its skin benefit capabilities, may also be included with the hydroquinone **composition**.

SUMM [0018] One embodiment of the invention is a **composition** which comprises hydroquinone (about 1% to about 12%, preferably about 2% to about 10%, more preferably about 2% to about 8%, more preferably with about 2% to about 4%, and most preferably about 3% to about 4%) and has a neutral **pH** of from about 5.5 to about 8.0, more preferably a **pH** of from about 5.5 to about 7.5, and most preferably at a

pH of from about 6.0 to about 7.5. This **composition** is color stabilized and cosmetically elegant. Antioxidants in the hydroquinone phase are instrumental in stabilizing the color of the hydroquinone **composition**. The most preferred example of such an antioxidant is sodium metabisulfite. Exceptional antioxidant qualities are seen at 0.10% (all percentages in the application are weight percent) and above, preferably from about 0.05% to about 0.5% for sodium metabisulfite.

SUMM [0019] Also in this embodiment is a cationic salt of acidic ascorbyl esters, which further helps to maintain the acceptable color desired in the hydroquinone **composition**. Cationic salts of acidic ascorbyl esters, including inorganic salts, preferably **magnesium ascorbyl phosphate**, and amino acyl derivatives, preferably aminopropyl ascorbyl phosphate, are preferred in this invention.

SUMM [0020] **Magnesium ascorbyl phosphate** (also called magnesium ascorbityl phosphate or magnesium L-ascorbyl-2-phosphate) has a chemical formula of C.sub.6H.sub.60.sub.9P-3/2 Mg. **Magnesium ascorbyl phosphate** has been available as an antioxidant and a melanin inhibitor for use in formulations of **pH** about 7.0 to 8.5. Hydroquinone has been used in **compositions** of a **pH** of about 2.0 to 4.0. In this invention, hydroquinone and **magnesium ascorbyl phosphate** may be used in neutral **pH** ranges without exhibiting excessive discoloration preferably for greater than about six months, more preferably for greater than about twelve months, and most preferably for greater than about eighteen months, or physical instability. The amount of **magnesium ascorbyl phosphate** is this embodiment of the invention is about 0.25% to about 3%, preferably about 0.25% to about 1%, most preferably at least about 0.5%.

SUMM [0021] In another embodiment, sodium metabisulfite and **magnesium ascorbyl phosphate** are used in about 0.01% (preferably from about 0.05% to about 0.5%, most preferably at least about 0.1%,) and about 0.5% (preferably from about 0.25% to about 3%, more preferably from about 0.25% to about 1%, and most preferably at least about 0.5%) respectively in a **composition** with about 4% hydroquinone. Although about 0.01% sodium metabisulfite without **magnesium ascorbyl phosphate** may not color stabilize an about 4% hydroquinone **composition**, and about 0.5% **magnesium ascorbyl phosphate** without sodium metabisulfite may not either, the combination of sodium metabisulfite and **magnesium ascorbyl phosphate** in these percentages is effective to stabilize the color of the about 1% to about 12%, about 2% to about 10%, preferably about 2% to about 8% and more preferably about 3% to about 4% and most preferably 4% hydroquinone **composition**.

SUMM [0022] In another embodiment of the invention, hydroquinone and a protected retinoid are both combined in the **composition**. Retinoids, in particular retinoic acid, retinal, and their derivatives, isomers and analogs (such as adapalene, tazarotene and isotretoin), are beneficial for improving rough skin texture, mottled pigmentation, sallow complexion, lines and wrinkles. Forms of retinoids have been developed wherein the retinoid is protected by a protective system. The protective system can be an entrapment system, a single or multi-laminar system, such as by formation of vesicle, such as a liposome, or by utilizing wax, paraffin, silicone, polyethylene or any material or system which protects the retinoid from oxidation. The preferred protected retinoid is in the form of small beads or vesicles which are of a form that can be adjusted to be incorporated into varied topical

compositions. One skilled in the art is familiar with the known protective system technologies, such as encapsulation and entrapment methodologies. A preferred embodiment utilizes encapsulation. For use herein, the encapsulation forms a protective system to prohibit or inhibit the oxidation of the retinoid. As utilized herein, the inhibition of the retinoid oxidation should be sufficient to prohibit browning of the **composition** for its shelf life, preferably greater than about six months, more preferably greater than about twelve months, and most preferably greater than about eighteen months. Examples of suitable methods of encapsulation include encapsulation by liposomes, wax, paraffin or any material or combination of materials which protect the retinoid from exposure to oxygen and inhibit oxidation of the retinoid from oxidation. Preferably, the protected retinoid, in particular retinoic acid, retinal, and their derivatives, isomers and analogs (such as adapalene, tazarotene and isotretoin), is in the form of small beads or spheres suitable for incorporation into a topical **composition**. The preferred form of protected retinol is manufactured by SunSmart (also known as Particle Sciences, Inc. of Bethlehem, Pa.) under the brand name of SunCaps A-1283. Retinoids are included from about 0.01% to about 5%, preferably from about 0.025% to about 2%, more preferably 0.05% to about 1.0%, and most preferably from about 0.025% to about 0.5%.

SUMM [0023] The color stability of the hydroquinone **composition** is promoted by one or more antioxidants in the hydroquinone phase, preferably sulfite, including but not limited to sulfites, bisulfites, metabisulfites, their salts and their derivatives, most preferably sodium metabisulfite, and a cationic salt of acidic ascorbyl esters, most preferably **magnesium ascorbyl phosphate** . While the hydroquinone is effective for the pigmentation disorder treatment, retinoid is used for its skin treatment benefits.

SUMM [0024] **Compositions** according to this invention may include dermatologically acceptable carriers. Such carriers are widely known in the art and deliver the **composition**'s ingredients to the skin without excessive degradation, inactivation or other unwanted interaction. An acceptable carrier also possesses suitable aesthetic and cosmetic qualities and may include emollients, conditioners and the like. **Compositions** according to this invention may include additives or components to enhance the skin penetration of its ingredients. They may also include ingredients with other therapeutic actions, such as anti-inflammatories, antibiotics, exfoliants and peels.

SUMM [0025] Tests, which results are detailed in the following two tables, are performed to show how well sodium metabisulfite ("SMBS") stabilizes color at each **pH** at 5.degree. C. and 40.degree. C. in 4% hydroquinone ("HQ") **compositions**.

TABLE I

Color Stability of 4% HQ **Compositions** with varying **pH** and % Sodium Metabisulfite at 5.degree. C. and 40.degree. C.

Result of **pH**-VS-SMBS Concentration

pH/SMBS %	3.50	4.00	4.50	5.00	5.50	6.00	6.50	7.00
5.degree. C.								
0.00	3	3	3	3	4	5	8	9
0.01	0	0	0	0	0	2	5	8
0.05	0	0	0	0	0	0	0	0
0.10	0	0	0	0	0	0	0	0
0.15	0	0	0	0	0	0	0	0
0.20	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0
40.degree. C.								

0.00	7	7	7	8	8	8	9	10
0.01	0	0	5	6	7	7	9	9
0.05	0	0	0	0	0	0	4	0
0.10	0	0	0	0	0	0	0	0
0.15	0	0	0	0	0	0	0	0
0.20	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0

Color Scale Legend
0 water white (no color)
1 extremely light straw (only a slight variation from water white)
2 light straw yellow
3 medium straw yellow
4 draw straw yellow
5 light amber
6 medium amber
7 dark amber
8 light brown
9 medium brown
10 dark brown

SUMM [0026] Table I shows that at 5.degree. C., 4% hydroquinone **compositions** maintain their white color with the addition of at least about 0.01% sodium metabisulfite at the low **pH** ranges (from about 3.50 to about 5.50) and at least 0.05% sodium metabisulfite for **pH** about 6.0 to about 7.0.

SUMM [0027] At 40.degree. C., 4% hydroquinone **compositions** have the same color stability with slightly more sodium metabisulfite, at least about 0.01% at about 3.5 to about 4.0 **pH**; at least about 0.05% sodium metabisulfite at about 4.5 to about 6.0 **pH**; and at least about 0.10% sodium metabisulfite at about 6.5 to about 7.0 **pH**.

SUMM **Magnesium Ascorbyl Phosphate** Concentration Testing

SUMM [0028] Tests, which results are detailed in the following two tables, are performed at 5.degree. C. and 40.degree. C. for certain percentages of **magnesium ascorbyl phosphate** at specific **pHs**. An improvement in the color stability of the 4% hydroquinone **compositions** is seen at and above 2.0% **magnesium ascorbyl phosphate** in the 6-7 **pH** range.

TABLE II

Color Stability of 4% HQ **Compositions** with varying **pH** and % **Magnesium Ascorbyl Phosphate** at 5.degree. C. and 40.degree. C.

Result of **pH**-VS-MAP Concentration

pH/MAP %	3.50	4.00	4.50	5.00	5.50	6.00	6.50	7.00
0.0	3	3	3	4	4	5	8	9
0.5	1	2	2	2	2	3	4	3
1.0	1	2	2	2	2	3	3	2
1.5	1	2	2	3	3	4	3	2
2.0	1	2	2	3	3	4	3	2
2.5	0	2	2	3	4	4	3	3
3.0	0	2	2	3	4	4	3	3
40.degree. C.								
0.0	7	7	7	8	8	8	9	10
0.5	7	7	7	7	8	8	7	7

1.0	6	7	7	7	6	7	6	6
1.5	6	7	7	7	7	5	5	5
2.0	4	5	5	7	5	5	4	4
2.5	4	6	6	7	5	5	4	4
3.0	4	5	6	6	4	5	4	4

Color Scale Legend
0 water white (no color)
1 extremely light straw (only a slight variation from water white)
2 light straw yellow
3 medium straw yellow
4 dark straw yellow
5 light amber
6 medium amber
7 dark amber
8 light brown
9 medium brown
10 dark brown

SUMM [0029] Table II shows that at 5.degree. C., 4% hydroquinone **compositions** maintain their white or light straw color with the addition of at least about 0.5% **magnesium ascorbyl phosphate** at the low **pH** ranges (from about 3.50 to about 5.50) and when about 1.0 to about 2.0% **magnesium ascorbyl phosphate** is used in the **pH** range of about 7.0. Color stability improvement is evident at all levels. 0.5% **magnesium ascorbyl phosphate** protected at **pH** 6.0-7.0, 1.0-1.5% at **pH** 5.5-7.0, and 2.0-3.0% at **pH** 3.5-7.0.

SUMM [0030] At 40.degree. C., 4% hydroquinone **compositions** are more likely to excessively discolor and **magnesium ascorbyl phosphate** helps to stabilize the color, by preventing the brownish black discoloration and maintaining an amber color. This is seen at about a **pH** of 3.50 with at least about 2.0% **magnesium ascorbyl phosphate**, and again at a **pH** of about 6.5 to about 7.0 with at least about 2.0% **magnesium ascorbyl phosphate**.

DETD [0031] A specific embodiment of the invention is listed in the following table. The **composition** is preferably formulated in separate phases as designated below.

Trade Name	CTFA Name	Percent
PHASE A		
Purified Water	Purified Water	45.07
PHASE B		
Carbomer 940	Carbomer	0.03
Disodium EDTA	Disodium EDTA	0.10
Sodium Citrate	Sodium Citrate	0.18
PHASE C		
Lecinol S-10	Hydrogenated Lecithin	0.75
PHASE D		
Phenyl Trimethicone	Phenyl Trimethicone	4.00
Gransil GCM-5	Cyclopentasiloxane, Polysilicone-11	2.50
CK-100	Dimethiconol	0.39
PHASE E		
Linoleic Acid	Linoleic Acid	2.50
Cetyl alcohol	Cetyl alcohol	2.75
Lipomulse 165	Glyceryl Stearate (and) PEG-100 Stearate	3.20

Cosmowax J	Cetearyl Alcohol (and) Ceteareth	1.50
BHT	Butylated Hydroxytoluene	0.05
Vitamin E Acetate	Tocopheryl Acetate	0.75
PHASE F		
Sepigel 305	Polyacrylamide (and) C 13-14 isoparaffin (and) laureth-7	1.75
PHASE G		
Purified Water	Purified Water	2.00
Sodium Metabisulfite	Sodium Metabisulfite	0.25
PHASE H		
Purified Water	Purified Water	3.00
VC-PMGU	Magnesium L-Ascorbyl Phosphate	0.50
PHASE I		
Purified Water	Purified Water	5.00
Alcohol SDA 40, 200 Proof	Alcohol	3.00
Glycerin 99% USP	Glycerin 99% USP	4.00
Hydroquinone	Hydroquinone	4.00
PHASE J		
Purified Water	Purified Water	1.00
Triethanolamine 99%	Triethanolamine 99%	0.60
PHASE K		
Benzyl Alcohol	Benzyl Alcohol	0.50
Fragrance MAIDA J-9145	Fragrance	0.03
Phenoxetol	Phenoxyethanol	0.60
PHASE L		
Suncaps A-1283	Water, Soybean (Glycine Soja) Oil, Carnuaba (Copernicia Cerifera), wax, tocopherol, retinol, Ceteareth-20	10.00

CLM What is claimed is:

1. A **composition** for the treatment of pigmentation disorders comprising: hydroquinone; and a cationic salt of acidic ascorbyl esters, said **composition** having a **pH** of about 5.5 to about 8.0.

2. The **composition** of claim 1 wherein the **pH** is about 5.5 to about 7.5.

3. The **composition** of claim 1 wherein the **pH** is about 6.0 to about 7.5.

4. The **composition** of claim 1 wherein the hydroquinone is present in about 1 to about 12%.

5. The **composition** of claim 1 wherein the hydroquinone is present in about 2 to about 10%.

6. The **composition** of claim 1 wherein the hydroquinone is present in about 2 to about 8%.

7. The **composition** of claim 1 wherein the hydroquinone is present in about 3 to about 4%.

8. The **composition** of claim 1 wherein the hydroquinone is present in about 4%.

9. The **composition** of claim 1 further comprising a water-soluble antioxidant.

10. The **composition** of claim 9 wherein the antioxidant comprises a sulfite.

11. The **composition** of claim 9 wherein the antioxidant

comprises sodium metabisulfite.

12. The **composition** of claim 11 wherein the sodium metabisulfite is present in at least about 0.05%.

13. The **composition** of claim 11 wherein the sodium metabisulfite is present at about 0.05% to about 0.5%.

14. The **composition** of claim 1 wherein the cationic salt comprises an inorganic salt.

15. The **composition** of claim 1 wherein the cationic salt comprises **magnesium ascorbyl phosphate**.

16. The **composition** of claim 15 wherein the **magnesium ascorbyl phosphate** is present in at least about 0.1%.

17. The **composition** of claim 15 wherein the **magnesium ascorbyl phosphate** is present at about 0.25 to about 3%.

18. The **composition** of claim 15 wherein the **magnesium ascorbyl phosphate** is present at about 0.25 to about 1%.

19. The **composition** of claim 9 wherein the antioxidant comprises sodium metabisulfite and the cationic salt comprises **magnesium ascorbyl phosphate**.

20. The **composition** of claim 19 wherein the sodium metabisulfite is present in at least about 0.05% and the **magnesium ascorbyl phosphate** is present in at least about 0.5%.

21. The **composition** of claim 1 wherein the cationic salt comprises an amino acyl derivative.

22. The **composition** of claim 21 wherein the cationic salt comprises aminopropyl ascorbyl phosphate.

23. The **composition** of claim 1 wherein the cationic salt comprises a sodium ascorbyl phosphate.

24. A skin benefit **composition** comprising: hydroquinone; a cationic salt of acidic ascorbyl esters, and a protected retinoid, said **composition** having a **pH** of about 5.5 to about 8.0.

25. The **composition** of claim 24 wherein the **pH** is about 5.5 to about 7.5.

26. The **composition** of claim 24 wherein the **pH** is about 6.0 to about 7.5.

27. The **composition** of claim 24 wherein the hydroquinone is present in about 1 to about 12%.

28. The **composition** of claim 24 wherein the hydroquinone is present in about 2 to about 10%.

29. The **composition** of claim 24 wherein the hydroquinone is present in about 2 to about 8%.

30. The **composition** of claim 24 wherein the hydroquinone is present in about 3 to about 4%.

31. The **composition** of claim 24 wherein the hydroquinone is present in about 4%.

32. The **composition** of claim 24 further comprising a water-soluble antioxidant.

33. The **composition** of claim 32 wherein the antioxidant comprises a sulfite.

34. The **composition** of claim 33 wherein the antioxidant comprises sodium metabisulfite.

35. The **composition** of claim 34 wherein the sodium metabisulfite is present in at least about 0.05%.

36. The **composition** of 34 wherein the sodium metabisulfite is present at about 0.05% to about 0.5%.

37. The **composition** of claim 24 wherein the cationic salt comprises an inorganic salt.

38. The **composition** of claim 24 wherein the cationic salt comprises **magnesium ascorbyl phosphate**.

39. The **composition** of claim 38 wherein the **magnesium ascorbyl phosphate** is present in at least about 0.1%.

40. The **composition** of claim 38 wherein the **magnesium ascorbyl phosphate** is present at about 0.25 to about 3%.

41. The **composition** of claim 38 wherein the **magnesium ascorbyl phosphate** is present at about 0.25 to about 1%.

42. The **composition** of claim 32 wherein the antioxidant comprises sodium metabisulfite and the cationic salt comprises **magnesium ascorbyl phosphate**.

43. The **composition** of claim 42 wherein the sodium metabisulfite is present in at least about 0.05% and the **magnesium ascorbyl phosphate** is present in at least about 0.5%.

44. The **composition** of claim 24 wherein the cationic salt comprises an amino acyl derivative.

45. The **composition** of claim 44 wherein the cationic salt comprises aminopropyl ascorbyl phosphate.

46. The **composition** of claim 24 wherein the cationic salt comprises a sodium ascorbyl phosphate.

47. The **composition** of claim 24 wherein the protected retinoid is protected with a protective system.

48. The **composition** of claim 24 wherein the protected retinoid comprises at least one of the group consisting of retinoic acid, retinol, retinal, retinoid analogues, isotretoin and its isomers.

49. The **composition** of claim 24 wherein the retinoid is present from about 0.01% to about 5.0%.

50. The **composition** of claim 24 wherein the retinoid is present from about 0.025% to about 2.0%.

51. The **composition** of claim 24 wherein the retinoid is present from about 0.05% to about 1.0%.

52. The **composition** of claim 24 wherein the retinoid is present from about 0.025% to about 0.5%.

53. A **composition** for the treatment of pigmentation disorders, said **composition** having a neutral **pH**, comprising: 4% hydroquinone; at least about 0.5% **magnesium ascorbyl phosphate**; at least about 0.1% Sodium metabisulfite; and an protected retinoid.

54. A method of stabilizing a hydroquinone **composition** having a **pH** of about 5.5 to about 8.0 comprising: Adding a cationic salt of acidic ascorbyl esters.

55. The method of claim 54 wherein the **pH** is about 5.5 to about 7.5.

56. The method of claim 54 wherein the **pH** is about 6.0 to about 7.5.

68. The method of claim 54 wherein the cationic salt comprises **magnesium ascorbyl phosphate**.

69. The method of claim 68 wherein the **magnesium ascorbyl phosphate** is present in at least about 0.1%.

70. The method of claim 68 wherein the **magnesium ascorbyl phosphate** is present at about 0.25 to about 3%.

71. The method of claim 68 wherein the **magnesium ascorbyl phosphate** is present at about 0.25 to about 1%.

72. The method of claim 62 wherein the antioxidant comprises sodium metabisulfite and the cationic salt comprises **magnesium ascorbyl phosphate**.

73. The method of claim 72 wherein the sodium metabisulfite is present in at least about 0.05% and the **magnesium ascorbyl phosphate** is present in at least about 0.5%.

77. A method of stabilizing a hydroquinone **composition** having a **pH** of about 5.5 to about 8.0 comprising: adding a cationic salt of acidic ascorbyl esters; and adding an protected retinoid.

78. The method of claim 81 wherein the **pH** is about 5.5 to about 7.5.

79. The method of claim 77 wherein the **pH** is about 6.0 to about 7.5.

91. The method of claim 77 wherein the cationic salt comprises **magnesium ascorbyl phosphate**.

92. The method of claim 91 wherein the **magnesium ascorbyl phosphate** is present in at least about 0.1%.

93. The method of claim 91 wherein the **magnesium**

ascorbyl phosphate is present at about 0.25 to about 3%.

94. The method of claim 91 wherein the **magnesium ascorbyl phosphate** is present at about 0.25 to about 1%.

95. The method of claim 85 wherein the antioxidant comprises sodium metabisulfite and the cationic salt comprises **magnesium ascorbyl phosphate**.

96. The method of claim 95 wherein the sodium metabisulfite is present in at least about 0.05% and the **magnesium ascorbyl phosphate** is present in at least about 0.5%.

106. The process of making a stable hydroquinone **composition** having a **pH** of about 5.5 to about 8.0 comprising: combining the following ingredients, in a carbon dioxide atmosphere: first, **magnesium ascorbyl phosphate** and sodium metabisulfite, then second, sodium metabisulfite, then third, **magnesium ascorbyl phosphate**, then fourth, hydroquinone; and wherein said ingredients are contained in suitable dermatologically acceptable carriers.

IT 50-81-7D, Ascorbic acid, esters 68-26-8, Retinol 116-31-4, Retinal **123-31-9**, Hydroquinone, biological studies 302-79-4, Retinoic acid 4759-48-2, Isotretinoin 7681-57-4, Sodium metabisulfite 113170-55-1 220644-17-7
(hydroquinone compns. for the treatment of pigmentation disorders and methods for their manuf.)

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TITLE: **Compositions** for the treatment of pigmentation disorders and methods for their manufacture
INVENTOR(S): Wortzman, Mitchell S., Scottsdale, AZ, UNITED STATES
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003053968	A1	20030320
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DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WILLIAM J. MCNICHOL, JR., ESQ., REED SMITH LLP, 2500 One Liberty Place, 1650 Market Street, Philadelphia, PA, 19103
NUMBER OF CLAIMS: 106
EXEMPLARY CLAIM: 1
LINE COUNT: 712
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L72 ANSWER 4 OF 10 USPATFULL
TI Method for slowing the decomposition of a cosmetic **composition**
AB A cosmetic **composition** includes a carrier, a skin-whitening agent, and sodium magnesium silicate. The sodium magnesium silicate is present in an amount effective to slow decomposition of the **composition**. A method of slowing the decomposition of a cosmetic **composition** containing a skin-whitening agent includes adding an effective amount of a sodium magnesium silicate to the **composition**.
SUMM [0001] The present invention relates to a cosmetic **composition**

for external use containing a carrier, a skin-whitening agent, and sodium magnesium silicate.

SUMM [0002] Certain skin-whitening agents in cosmetic **compositions** oxidize over time, causing the cosmetic **composition** to decompose. The decomposition causes the cosmetic **composition** to darken and to develop an intense, undesirable odor. Certain skin-whitening ingredients are known to be worse than others for premature oxidation. For example, **magnesium ascorbyl phosphate** and botanical whiteners such as bearberry extract and others have been especially prone to premature oxidation. For this reason, cosmetic **compositions** containing these whitening agents tend to decompose, turn brown, and develop a foul odor. As a result, cosmetic **compositions** containing certain skin-whitening agents have very limited shelf lives.

SUMM [0003] Nevertheless, skin-whitening **compositions** are still in high demand, especially in Asian markets. For this reason, a method is needed to slow the decomposition of skin-whitening **compositions** and the resulting darkening and foul odor of the skin-whitening **compositions**. Surprisingly, adding sodium magnesium silicate to skin-whitening **compositions** dramatically slows the darkening of these **compositions** as well as the development of the undesirable odor. Accordingly, cosmetic **compositions** that contain skin-whitening agents susceptible to oxidation have longer shelf lives if those cosmetic **compositions** also contain sodium magnesium silicate.

SUMM [0004] In one aspect of the invention, a **composition** for topical use that has a melanin synthesis-inhibiting activity is provided. The **composition** comprises a carrier, a skin-whitening agent, and sodium magnesium silicate, wherein the sodium magnesium silicate is present in an amount effective to slow decomposition of the **composition**.

SUMM [0005] In another aspect of the invention, an improvement in a skin-whitening **composition** comprises an effective amount of sodium magnesium silicate to slow the decomposition of the **composition**.

SUMM [0006] In still another aspect of the invention, a method of slowing the decomposition of a cosmetic **composition** containing a skin-whitening agent comprises adding an effective amount of a sodium magnesium silicate to the **composition**.

DETD [0009] In accordance with the present invention, a skin-whitening cosmetic **composition** is provided that comprises a carrier, a skin-whitening agent, and sodium magnesium silicate. The present invention also concerns preventing the premature oxidation of skin-whitening agents in cosmetic **compositions**, which causes the **compositions** to brown and to develop an odor over time.

DETD [0010] Certain skin-whitening agents are especially prone to premature oxidation. These skin-whitening agents include, but are not limited to, **magnesium ascorbyl phosphate** and botanical extracts such as bearberry extract, lemon extract, cucumber extract, mulberry extract, licorice extract.

DETD [0011] The cosmetic **composition** may contain other skin-whitening agents, whether or not those agents are prone to premature oxidation. Such skin-whitening agents may include all the known whitening agents and those that may be developed in the future. Although it is not possible to identify and list all known skin-whitening agents, the following skin-whitening agents may be included in the cosmetic **composition** of the present invention: tyrosinase inhibitors, free radical scavengers, chelating agents, and

mixtures thereof.

DETD [0015] Non-exclusive examples of the esters are, for instance, kojic acid monoesters such as kojic acid monobutyrate, kojic acid monocaprate, kojic acid monopalmitate, kojic acid monostearate, kojic acid monocinnamoate and kojic acid monobenzoate; kojic acid diesters such as kojic acid dibutyrate, kojic acid dipalmitate, kojic acid distearate and kojic acid dioleate. A preferred monoester is an ester in which an OH group at 5-position of kojic acid is esterified. Esterification can improve stabilities against **pH** or sun light, while maintaining a melanin synthesis-inhibiting activity equal to that of kojic acid.

DETD [0018] Non-exclusive examples of the vitamin C derivatives are, for instance, the alkyl esters of L-ascorbic acid where the alkyl portion has from 8 to 20 carbon atoms. For example, such esters include, but are not limited to L-ascorbyl palmitate, L-ascorbyl isopalmitate, L-ascorbyl dipalmitate, L-ascorbyl isostearate, L-ascorbyl distearate, L-ascorbyl diisostearate, L-ascorbyl myristate, L-ascorbyl isomyristate, L-ascorbyl 2-ethylhexanoate, L-ascorbyl di-2-ethylhexanoate, L-ascorbyl oleate and L-ascorbyl dioleate, tetrahexyl decyl ascorbate; phosphates of L-ascorbic acid such as L-ascorbyl-2-phosphate and L-ascorbyl-3-phosphate; sulfates of L-ascorbic acid such as L-ascorbyl-2-sulfate and L-acorbyl-3-sulfate; their salts with alkaline earth metals such as calcium and magnesium. A preferred whitener is **magnesium ascorbyl phosphate**. The vitamin C derivatives can be used alone or in a mixture of two or more.

DETD [0021] The skin-whitening agent may be used in the cosmetic **composition** of the present invention in an amount of from about 0.001% to about 99%. Preferably, the skin-whitening agent is present in the **composition** in an amount of from about 0.01% to about 20%. More preferably, the amount ranges from about 0.1% to about 10%.

DETD [0022] Sodium magnesium silicate is commercially available under the trade name LAPONITE. It is a synthetic silicate clay with a **composition** mainly of magnesium and sodium silicate.

DETD [0023] Surprisingly, sodium magnesium silicate has the unexpected and beneficial effect of reducing the time and temperature-induced darkening effect of the skin-whitening agent in the cosmetic **composition** . In other words, sodium magnesium silicate prevents the premature darkening of the cosmetic **composition**. The results are especially impressive when the cosmetic **composition** includes skin-whitening agents prone to oxidation such as **magnesium ascorbyl phosphate** and botanical extracts.

DETD [0024] Surprisingly, sodium magnesium silicate also improves the odor of the **composition** by reducing the time and temperature-induced development of foul odors as the skin-whitening agents oxidize. In other words, sodium magnesium silicate prevents the premature development of a foul odor. The results are especially impressive when the cosmetic **composition** includes skin-whitening agents prone to oxidation such as **magnesium ascorbyl phosphate** and botanical extracts.

DETD [0025] Sodium magnesium silicate may be used in the whitening **composition** in an amount from about 0.001% to about 99%. Preferably, sodium magnesium silicate is present in the **composition** in an amount of from about 0.01% to about 10%. More preferably, the amount ranges from about 0.1% to about 5%.

DETD [0026] The cosmetic **compositions** of the present invention may be prepared in various forms. For example, they may be in the form of a cosmetic **preparation** such as an emulsion, liniment or ointment lotions, creams, (both oil-in-water, water-in-oil, and multiple phase), solutions, suspensions (anhydrous and water based), anhydrous products (both oil and glycol based), gels, sticks, surfactant systems (cleansers, shampoos, facial washes, etc.), powders, masks, pack or powder, or the like.

DETD [0027] The cosmetic **compositions** of the present invention generally include a cosmetically acceptable or pharmaceutically acceptable carrier. The terms "pharmaceutically acceptable" and

"cosmetically acceptable" means those drugs, medicaments, or inert ingredients which are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, incompatibility, instability, irritation, and the like, commensurate with a reasonable benefit/risk ratio.

DETD [0028] The carrier usually forms from about 1% to about 99.9%, preferably from about 50% to about 99% by weight of the **composition**, and can, in the absence of other cosmetic adjuncts, form the balance of the **composition**.

DETD [0029] Other optional ingredients can be included in the cosmetic **composition** of the present invention. As a non-limiting illustration, the optional ingredients can include UV absorbers, fragrances, preservatives, thickeners, **ph** adjusters, etc, so long as they do not interfere with the function of the skin-whitening agent and the sodium magnesium silicate.

DETD [0030] Following are examples of **compositions** made according to the present invention. The examples are merely illustrative; they are not limiting.

DETD [0031] Each example was compared with a "control" cosmetic **composition** that had all the same ingredients as the example except for sodium magnesium silicate. The cosmetic **composition** of each example was then qualitatively compared to its control cosmetic **composition** after exposure to the same conditions.

DETD [0032]

Ingredient	Weight Percent
Laponite XLG (Sodium Magnesium Silicate)	0.50
Magnesium Ascorbyl Phosphate 3.00	
Botanical whitening complex	1.00
Water and Optional Ingredients	q.s.

DETD [0033] The **composition** of Example 1 was qualitatively compared to its control **composition** after 30 days at 50.degree. C. The control **composition** decomposed, changed its color to brown, and began developing a foul odor, as expected. Surprisingly, the **composition** of Example 1 maintained its pleasant odor and appearance.

DETD [0035] The **composition** of Example 2 was qualitatively compared to its control **composition** after 30 days at 50.degree. C. The control **composition** decomposed, changed its color to brown, and began developing a foul odor, as expected. Surprisingly, the **composition** of Example 2 maintained its pleasant odor and appearance.

DETD [0036]

Ingredient	Weight Percent
Laponite XLG (Sodium Magnesium Silicate)	1.00
Magnesium Ascorbyl Phosphate 3.00	
Vitamin E	0.05
Water and Optional Ingredients	q.s.

DETD [0037] The **composition** of Example 3 was qualitatively compared to its control **composition** after 30 days at 50.degree. C. The control **composition** decomposed, changed its color to brown, and began developing a foul odor, as expected. Surprisingly, the **composition** of Example 3 maintained its pleasant odor and appearance.

DETD [0038] Based on the above results, the addition of **magnesium ascorbyl phosphate** to a cosmetic **composition** containing a skin-whitening agent prone to premature oxidation will

extend the shelf life of that cosmetic **composition**. **Magnesium ascorbyl phosphate** may extend the shelf life of the cosmetic by as much as 25%, preferably by as much as 50%, more preferably by as much as 100%, or most preferably by as much as 200%.

CLM What is claimed is:

1. A **composition** for topical use that has a melanin synthesis-inhibiting activity, the **composition** comprising a carrier, a skin-whitening agent, and sodium magnesium silicate, wherein the sodium magnesium silicate is present in an amount effective to slow decomposition of the **composition**.

2. The **composition** of claim 1 wherein the sodium magnesium silicate is present in an amount effective to prevent premature darkening of the cosmetic **composition** and to prevent premature development of a foul odor.

3. The **composition** of claim 1 wherein the skin-whitening agent is selected from the group consisting of tyrosinase inhibitors, free radical scavengers, chelating agents, and mixtures thereof.

4. The **composition** of claim 1 wherein the skin-whitening agent is selected from the group consisting of bearberry extract, lemon extract, cucumber extract, mulberry extract, licorice extract, lactic acid, acerola fermentate, **magnesium ascorbyl phosphate**, and mixtures thereof.

5. The **composition** of claim 1 wherein the **composition** has a color and the sodium magnesium silicate is present in an amount effective to prevent premature darkening of the color and to prevent premature development of a foul odor.

6. The **composition** of claim 1 wherein the sodium magnesium silicate is present in an amount effective to stabilize the viscosity of the **composition**.

7. The **composition** of claim 1 wherein the **composition** comprises from about 0.01% to about 20% by weight of skin-whitening agent.

8. The **composition** of claim 1 wherein the **composition** comprises from about 0. 1% to about 10% by weight of skin-whitening agent.

9. The **composition** of claim 1 wherein the **composition** comprises from about 0.001% to about 99% by weight of the sodium magnesium silicate.

10. The **composition** of claim 1 wherein the **composition** comprises from about 0.01% to about 10% by weight of the sodium magnesium silicate.

11. The **composition** of claim 1 wherein the **composition** is in the form selected from the group consisting of cream, ointment, foam, lotion, plaster, tablets, granules, and emulsion.

12. In a skin-whitening **composition** comprising a carrier and a skin-whitening agent, the improvement comprising an effective amount of sodium magnesium silicate to slow the decomposition of the **composition**.

13. A method of slowing the decomposition of a cosmetic **composition** containing a skin-whitening agent, the method comprising adding an effective amount of a sodium magnesium silicate to

the **composition**.

14. The method of claim 13 wherein the **composition** comprises from about 0.001% to about 99% by weight of a skin-whitening agent.

15. The method of claim 13 wherein the **composition** comprises from about 0.01% to about 10% by weight of the sodium magnesium silicate.

18. The method of claim 13 wherein the skin-whitening agent is selected from the group consisting of bearberry extract, lactic acid, acerola fermentate, **magnesium ascorbyl phosphate**, and mixtures thereof.

19. The method of claim 13 wherein the sodium magnesium silicate is present in an amount effective to prevent premature darkening of the cosmetic **composition** and to prevent premature development of a foul odor.

20. The method of claim 19 wherein the **composition** comprises from about 0.001% to about 99% by weight of the sodium magnesium silicate.

IT 50-21-5, Lactic acid, biological studies 50-81-7, Vitamin C, biological studies 52-90-4, L-Cysteine, biological studies 70-18-8, Glutathione, biological studies 70-49-5, Mercaptosuccinic acid **123-31-9**, Hydroquinone, biological studies 497-76-7, Arbutin 501-30-4, Kojic acid 42612-66-8, Mercaptodextran **108910-78-7**, Magnesium ascorbyl phosphate 227605-22-3, Laponite XLG
(sodium magnesium silicate for slowing decompn. of skin-whitening compns.)

ACCESSION NUMBER: 2002:258388 USPATFULL
TITLE: Method for slowing the decomposition of a cosmetic **composition**
INVENTOR(S): Zimmerman, Amy C., Grand Rapids, MI, UNITED STATES
Harris, Ruth Elaine, Belmont, MI, UNITED STATES
PATENT ASSIGNEE(S): AMWAY CORPORATION (U.S. corporation)

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DOCUMENT TYPE: Utility
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SUMM [0005] In the seeds of oilseed crops, which include economically important crops, such as soybean, rapeseed, sunflower and palm, the water insoluble oil fraction is stored in discrete subcellular structures variously known in the art as oil bodies, oleosomes, lipid bodies or spherosomes (Huang 1992, Ann. Rev. Plant Mol. Biol. 43: 177-200). Besides a mixture of oils (triacylglycerides), which chemically are defined as glycerol esters of fatty acids, oil bodies comprise phospholipids and a number of associated proteins, collectively termed oil body proteins. From a structural point of view, oil bodies

are considered to be a triacylglyceride matrix encapsulated by a monolayer of phospholipids in which oil body proteins are embedded (Huang, 1992, Ann. Rev. Plant Mol. Biol. 43: 177-200). The seed oil present in the oil body fraction of plant species is a mixture of various triacylglycerides, of which the exact **composition** depends on the plant species from which the oil is derived. It has become possible through a combination of classical breeding and genetic engineering techniques, to manipulate the oil profile of seeds and expand on the naturally available repertoire of plant oil **compositions**. For an overview of the ongoing efforts in his area, see Designer Oil Crops/Breeding, Processing and Biotechnology, D. J. Murphy Ed., 1994, VCH Verlagsgesellschaft, Weinheim, Germany.

SUMM [0009] The present invention relates to novel emulsion formulations which are prepared from oil bodies. The emulsion formulations of the subject invention are obtainable in non-toxic and food grade forms. In addition, the emulsion formulations are advantageously prepared from an oil body **preparation** which is creamy in texture and thus may be readily applied in a variety of products that are topically applied to the skin. The present inventors have found that the oil body fraction of living cells is useful in the formulation of personal care and dermatological products. Broadly stated, the present invention provides an emulsion formulation for topical application or for application to the surface area of the human body comprising washed oil bodies derived from a cell.

SUMM [0012] In a preferred embodiment of the invention, the washed oil body **preparation** is obtained from plant seeds, including seeds obtainable from flax, safflower, rapeseed, soybean, maize and sunflower. Accordingly, the invention provides a method for preparing an emulsion formulation for topical application from plant seeds comprising:

SUMM [0016] (d) washing the oil body phase to yield a washed oil body **preparation**; and

SUMM [0017] (e) formulating the washed oil body **preparation** into an emulsion for topical application.

SUMM [0019] In a further preferred embodiment of the invention, formulating the emulsion comprises stabilizing the washed oil body **preparation** to prevent degradation of the oil bodies either by physical forces or chemical forces.

SUMM [0020] The emulsions of the present invention can be used in a wide range of applications including in the **preparation** of personal care and dermatological products. Additional advantages and features of the present invention will become apparent after consideration of the accompanying drawings and the following detailed description of the invention.

DRWD [0021] FIG. 1 is a Coomassie blue stained gel of a washed oil body **preparation** from white mustard, rapeseed (Brassica napus), soybean, peanut, squash, flax, sunflower, safflower and maize.

DETD [0025] In a preferred embodiment of the invention, formulating the washed oil bodies comprises stabilization of the washed oil bodies so that an oil body **preparation** is obtained that is chemically as well as physically stable.

DETD [0031] (2) washing the oil body phase to yield a washed oil body **preparation**; and

DETD [0032] (3) formulating the washed oil body **preparation** into an emulsion for use in a product for use in a topical application.

DETD [0036] The term "washing the oil bodies" as used herein means any process that removes cellular contaminants from the oil body phase, in particular any contaminant which imparts undesirable properties to the

emulsion formulation, such as allergenic properties, undesirable color, odor, flavor or dermatological characteristics or any other undesirable property. Examples of methods of washing include gravitation based separation methods such as centrifugation and size exclusion based separation techniques such as membrane ultrafiltration and crossflow microfiltration. Washing methods and conditions are selected in accordance with the desired purity of the oil body **preparation**
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DETD [0037] The term "washed oil body **preparation**" as used herein means a **preparation** of oil bodies from which a significant amount of cellular material has been removed including contaminants which impart undesirable properties to the emulsion formulation, such as allergenic properties, undesirable color, odor, taste or organoleptic characteristics or any other undesirable property. Preferably, the washed oil body **preparation** contains less than about 75% (w/w) of all endogenously present non-oil body seed proteins, more preferably the washed oil body **preparation** contains less than about 50% (w/w) of endogenously present non-oil body seed proteins, even more preferably less than about 20% (w/w) of endogenously present non-oil body seed proteins and most preferably less than about 10%(w/w) of endogenously present non-oil body seed proteins.

DETD [0038] By "formulating the oil bodies into an emulsion for application to the body", it is meant that the washed oil body **preparation** is mixed, homogenized or prepared until an emulsion is formed In a preferred embodiment, an additional ingredient is added, such as a liquid phase, and the washed oil body **preparation** and the additional ingredient are mixed until a homogenous mixture is attained.

DETD [0040] The washed oil body **preparations** are particularly suitable for the formulation of emulsions for application to the surface area of the human body due to advantageous properties outlined below.

DETD [0042] The emulsion formulations of the present invention comprise substantially intact washed oil bodies of approximately uniform size, shape and density. When viewed under the electron microscope, oil bodies are found to be more or less spherically shaped structures (see: Example Murphy, D. J. and Cummins I., 1989, Phytochemistry, 28: 2063-2069; Jacks, T. J. et al., 1990, JAOCS, 67: 353-361). Typical sizes of oil bodies vary between 0.4 micrometer and 1.5 micrometer (Murphy, D. J. and Cummins I., 1989, Phytochemistry, 28: 2063-2069). When analyzed using a Malvern Size Analyzer, it was found that oil bodies in a washed oil body **preparation** isolated from rapeseed were symmetrically and unimodally distributed around 1 micrometer. Using a Malvern Size Analyzer a washed oil body **preparation** could be clearly distinguished from commercially obtainable oil-in-water emulsions including soymilk, mayonnaise (Kraft Real Mayonnaise) and two coconut milk **preparations** (Tosca, Aroy-D). The exact size and density of the oil bodies depends at least in part on the precise protein/phospholipid/triacylglyceride **composition** which is present. Preparing washed oil bodies according to the present invention does not result in a substantive alteration in the shape of the oil bodies in comparison with those present in whole seed when viewed under the electron microscope.

DETD [0044] The oil bodies present in the washed oil body **preparations** of the present invention are resistant to exposure to strong acids and bases, including prolonged exposure to acidic conditions at least as low as **pH** 2 and alkaline conditions at least as high as **pH** 10. When exposed to **pH** 12, a slight loss of oil was observed, indicating a loss of integrity of the oil body structure. In addition, extraction with various organic solutions, including methanol, ethanol, hexane, isopropyl alcohol and ethyl acetate, does not or only slightly compromise the integrity of the oil bodies present in the washed oil body **preparation**. The oil bodies present in the washed oil body **preparation** were also found to withstand mixing with the anionic detergent, sodium dodecyl sulfate (SDS), the cationic, detergent hexadecyl trimethyl bromide and

Tween-80, a non-ionic detergent. Boiling of the washed oil body **preparation** in the presence of SDS was found to result at least partly in disintegration of the oil body structure. The oil bodies present in the washed oil body **preparation** are stable when maintained for 2 hours up to at least 100.degree. C. A slow freeze and thaw of washed oil body **preparations** resulted in a change in their physical appearance characterized by the formation of clumps as opposed to a homogeneous emulsion. Oil body clumping following a freeze-thaw could also be prevented to a large degree by either a) flash freezing in liquid nitrogen instead of slow freezing at -20.degree. C. or b) adding glycerol in excess of 5% (v/v) to the oil body **preparation** prior to freezing. The resistance to relatively harsh chemical and physical conditions, is a unique characteristic of the oil bodies present in the washed oil body **preparation** of the subject invention.

DETD [0045] The present invention provides emulsion formulations comprising oil bodies from which a significant amount of seed contaminants have been removed. These contaminants include proteins, volatiles and other compounds which may impart undesirable color, odor, flavor, organoleptic characteristics or other undesirable characteristics. A number of seed proteins have been reported to cause allergenic reactions. For example, Ogawa et al. (1993, Biosci. Biotechnol. Biochem., 57:1030-1033) report allergenicity of the soybean glycoprotein P34 (alternatively referred to as Gly m Bd 30K). Allergenic reactions against rapeseed, wheat and barley seed proteins have also been reported (Armentia et al., 1993., Clin. Exp. Allergy 23: 410-415; Monsalve et al., 1993, Clin. Exp. Allergy 27: 833-841). Hence removal of contaminating seed proteins is advantageous. Washing conditions may be selected such that a substantially pure oil body **preparation** is obtained. In that case, only the oil body proteins are substantially present in the **preparation**.

DETD [0046] For many applications, it is also considered desirable that a purer better defined oil body **preparation** is obtained, as this allows more control over the formulation process of the final emulsion. In order for the washed oil body **preparation** to be included in a diverse set of emulsions it is desirable that volatiles are kept to a minimum and the color is preferably light or white. Washing of the oil body **preparation** results in a lighter colored **preparation**. In addition, a substantial amount of volatiles is removed. Also removed by washing are compounds which promote the growth of microorganisms as it was observed that a washed oil body **preparation** had a longer shelf life than an unwashed **preparation**. Other compounds which are removed by washing include anti-nutritional glucosinilates and/or breakdown products thereof and fibrous material. When heat treated to 60.degree. C. or 80.degree. C., it was observed that larger quantities of water remained absorbed by the washed oil body **preparation** when compared with an unwashed **preparation**. Upon cooling down to room temperature and centrifugation, it was observed that the washed oil body **preparation** remained stable, while phase separation occurred in the unwashed **preparation**. Given the enhanced stability of washed oil bodies, they are preferred where the formulation process involves the application of heat. When heated to 40.degree. C., the washed oil body **preparation** was able to absorb a larger quantity of exogenously added water without resulting in phase separation. Thus in the formulation of aqueous emulsions, washed oil bodies are preferred. The capacity to absorb exogenously added oils was also compared between a **preparation** of washed oil bodies and an unwashed **preparation**. Larger amounts of exogenous oil could be added to the washed oil body **preparation** before an unstable emulsion was formed. This is advantageous in formulations where exogenous oils or waxes are added in the formulation process such as where personal care products are prepared. When viscosity was compared between a washed oil body **preparation** and an unwashed

preparation it was found that the washed **preparation** was more viscous. A more viscous **preparation** of oil bodies is desirable as this allows for more flexibility in the formulation process and eliminates the need for the addition of thickening agents in the formulation process.

DETD [0047] Thus the washed oil body **preparation** provided here is superior to an unwashed **preparation** in many respects. The washed oil body **preparation** of the present invention is a better defined **preparation** with a longer shelf life and more preferable color, odor and viscosity characteristics. The washed oil body **preparation** also has superior water and oil absorption characteristics. Finally due to the removal of a significant amount of seed proteins, allergenic reactions are less likely to occur. These characteristics allow the use of the washed oil body **preparation** in the formulation of a variety of domestic and industrial emulsions.

DETD [0048] The above observations were made using washed and unwashed oil body **preparations** obtained from rapeseed and prepared as detailed in Example 2 of the present application. It is believed that resistance to relatively harsh chemical and physical conditions will be a characteristic of the oil bodies present in the washed oil **preparation** of the subject invention regardless of the source of the oil bodies. However one or more of the hereinbefore documented properties for rapeseed oil bodies may vary depending on the cells from which the washed oil bodies **preparation** is obtained. Nevertheless it is to be clearly understood that the subject invention is drawn to an oil body **preparation** which may be obtained from any cell comprising oil bodies.

DETD [0050] Sources and **Preparation** of the Oil Bodies

DETD [0051] The washed oil body **preparation** of the subject may be obtained from any cell containing oil bodies or oil body-like organelles. This includes animal cells, plant cells, fungal cells, yeast cells (Leber, R. et al., 1994, Yeast 10: 1421-1428), bacterial cells (Pieper-Furst et al., 1994, J. Bacteriol. 176: 4328-4337) and algae cells (Rossler, P. G., 1988, J. Physiol. (London) 24: 394-400).

DETD [0053] More preferably, the washed oil body **preparation** of the subject invention is prepared from plant seeds. Among the plant seeds useful herein preferred are those seeds obtainable from plant species selected from the group of plant species consisting of almond (Prunus dulcis); anise (Pimpinella anisum); avocado (Persea spp.); beach nut (Fagus sylvatica); borage (also known as evening primrose) (Boragio officinalis); Brazil nut (Bertholletia excelsa); candle nut (Aleuritis tiglium); carapa (Carapa guineensis); cashew nut (Ancardium occidentale); castor (Ricinus communis); coconut (Cocus nucifera); coriander (Coriandrum sativum); cottonseed (Gossypium spp.); crambe (Crambe abyssinica); Crepis alpina; croton (Croton tiglium); Cuphea spp.; dill (Anethum gravealis); Euphorbia lagascae; Dimorphoteca pluvialis; false flax (Camolina sativa); fennel (Foeniculum vulgaris); groundnut (Arachis hypogaea); hazelnut (coryllus avellana); hemp (Cannabis sativa); honesty plant (Lunnaria annua); jojoba (Simmondsia chinensis); kapok fruit (Ceiba pentandra); kukui nut (Aleuritis moluccana); Lesquerella spp., linseed/flax (Linum usitatissimum); macademia nut (Macademia spp.); maize (Zea mays); meadow foam (Limnanthes alba); mustard (Brassica spp. and Sinapis alba); oil palm (Elaeis guineeis); oiticia (Licania rigida); paw paw (Assimina triloba); pecan (Juglandaceae spp.); perilla (Perilla frutescens); physic nut (Gatropha curcas); pilinut (Canarium ovatum); pine nut (pine spp.); pistachio (Pistachia vera); pongam (Bongamin glabra); poppy seed (Papaver soniferum); rapeseed (Brassica spp.); safflower (Carthamus tinctorius); sesame seed (Sesamum indicum); soybean (Glycine max); squash (Cucurbita maxima); sal tree (Shorea rubusha); Stokes aster (Stokesia laevis); sunflower (Helianthus annuus); tukuma (Astocarya spp.); tung nut (Aleuritis cordata); vernonia (Vernonia galamensis); and mixtures thereof.

DETD [0056] Plants are grown and allowed to set seed using agricultural

cultivation practises well known to a person skilled in the art. After harvesting the seed and if desired removal of material such as stones or seed hulls (dehulling), by for example sieving or rinsing, and optionally drying of the seed, the seeds are subsequently processed by mechanical pressing, grinding or crushing. In a preferred embodiment, a liquid phase is added prior to or while grinding the seeds. This is known as wet milling. Preferably the liquid is water although organic solvents such as ethanol may also be used. Wet milling in oil extraction processes has been reported for seeds from a variety of plant species including: mustard (Aguilar et al 1990, Journal of Texture studies 22:59-84), soybean (U.S. Pat. No. 3,971,856; Carter et al., 1974, J. Am. Oil Chem. Soc. 51:137-141), peanut (U.S. Pat. Nos. 4,025,658; 4,362,759), cottonseed (Lawhon et al., 1977, J. Am. Oil, Chem. Soc. 63:533-534) and coconut (Kumar et al., 1995, INFORM 6 (11):1217-1240). It may also be advantageous to imbibe the seeds for a time period from about fifteen minutes to about two days in a liquid phase prior grinding. Imbibing may soften the cell walls and facilitate the grinding process. Imbibition for longer time periods may mimic the germination process and result in certain advantageous alterations in the **composition** of the seed constituents. Preferably the added liquid phase is water.

DETD [0057] The seeds are preferably ground using a colloid mill, such as the Mz130 (Fryma Inc.). Besides colloid mills, other milling and grinding equipment capable of processing industrial scale quantities of seed may also be employed in the here described invention including: flaking rolls, disk mills, colloid mills, pin mills, orbital mills, IKA mills and industrial scale homogenizers. The selection of the mill may depend on the seed throughput requirements as well as on the source of the seed which is employed. It is of importance that seed oil bodies remain substantially intact during the grinding process. Grinding of the seeds therefore results in the release of preferably less than about 50% (v/v) of the total seed oil content in the form of free oil, more preferably less than about 20% (v/v) and most preferably less than about 10% (w/w). Any operating conditions commonly employed in oil seed processing, which tend to disrupt oil bodies are unsuitable for use in the process of the subject invention. Milling temperatures are preferably between 10.degree. C. and 90.degree. C. and more preferably between 26.degree. C. and 30.degree. C., while the **pH** is preferably maintained between 2.0 and 10.

DETD [0059] Following the removal of insoluble contaminants, the oil body phase is separated from the aqueous phase. In a preferred embodiment of the invention a tubular bowl centrifuge is employed. In other embodiments, hydrocyclones, disc stack centrifuges, or settling of phases under natural gravitation or any other gravity based separation method may be employed. It is also possible to separate the oil body fraction from the aqueous phase employing size exclusion methods, such as membrane ultrafiltration and crossflow microfiltration. In preferred embodiments the tubular bowl centrifuge is a Sharples model AS-16 (Alpha Laval) or a AS-46 Sharples (Alpha Laval). A critical parameter is the size of the ring dam used to operate the centrifuge. Ring dams are removable rings with a central circular opening varying, in the case of the AS-16, from 28 to 36 mm and regulate the separation of the aqueous phase from the oil body phase thus governing the purity of the oil body fraction which is obtained. In preferred embodiments, a ring dam size of 29 or 30 mm is employed when using the AS-16. The exact ring dam size employed depends on the type of oil seed which is used as well as on the desired final consistency of the oil body **preparation**. The efficiency of separation is further affected by the flow rate. Where the AS-16 is used flow rates are typically between 750-1000 ml/min (ring dam size 29) or between 400-600 ml/min (ring dam size 30) and temperatures are preferably maintained between 26.degree. C. and 30.degree. C. Depending on the model centrifuge used, flow rates and ring dam sizes must be adjusted so that an optimal separation of the oil body fraction from the aqueous phase is achieved. These adjustments will be readily

apparent to a skilled artisan.

DETD [0061] The **compositions** obtained at this stage in the process, generally are relatively crude and comprise numerous endogenous seed proteins, which includes glycosylated and non-glycosylated proteins and other contaminants such as starch or glucosinilates or breakdown products thereof. The present invention comprises the removal of a significant amount of seed contaminants. To accomplish removal of contaminating seed material, the oil body **preparation** obtained upon separation from the aqueous phase is washed at least once by resuspending the oil body fraction and centrifuging the resuspended fraction. This process yields what for the purpose of this application is referred to as a washed oil body **preparation**. The number of washes will generally depend on the desired purity of the oil body fraction. Depending on the washing conditions which are employed, an essentially pure oil body **preparation** may be obtained. In such a **preparation** the only proteins present would be oil body proteins. In order to wash the oil body fraction, tubular bowl centrifuges or other centrifuges such hydrocyclones or disc stack centrifuges may be used. Washing of oil bodies may be performed using water, buffer systems, for example, sodium chloride in concentrations between 0.01 M and at least 2 M, 0.1 M sodium carbonate at high **pH** (11-12), low salt buffer, such as 50 mM Tris-HCl **pH** 7.5, organic solvents, detergents or any other liquid phase. In preferred embodiments the washes are performed at high **pH** (11-12). The liquid phase used for washing as well as the washing conditions, such as the **pH** and temperature, may be varied depending on the type of seed which is used. Washing at a number of different **pH**'s between **pH** 2 and **pH** 11-12 may be beneficial as this will allow the step-wise removal of contaminants, in particular proteins. Preferably washing conditions are selected such that the washed oil body **preparation** comprises less than about 75%(w/w) of all endogenously present non-oil body seed proteins, more preferably less than about 50% (w/w) of endogenously present non-oil body seed proteins even more preferably, less than 20% (w/w) of endogenously present non-oil body seed proteins, and most preferably less than about 10% (w/w) of endogenously present non-oil body proteins. Washing conditions are selected such that the washing step results in the removal of a significant amount of contaminants without compromising the structural integrity of the oil bodies. In embodiments where more than one washing step is carried out, washing conditions may vary for different washing steps. SDS gel electrophoresis or other analytical techniques may conveniently be used to monitor the removal of endogenous seed proteins and other contaminants upon washing of the oil bodies. It is not necessary to remove all of the aqueous phase between washing steps and the final washed oil body **preparation** may be suspended in water, a buffer system, for example, 50 mM Tris-HCl **pH** 7.5, or any other liquid phase and if so desired the **pH** may be adjusted to any **pH** between **pH** 2 and **pH** 10.

DETD [0062] The process to manufacture the washed oil body **preparation** may be performed in batch operations or in a continuous flow process. Particularly when tubular bowl centrifuges are used, a system of pumps operating between steps (a) and (b), (b) and (c), and (c) and (d) a continuous flow throughout the processing system is generated. In a preferred embodiment, the pumps are 1 inch M2 Wilden air operated double diaphragm pumps. In other embodiments, pumps, such as hydraulic or peristaltic pumps may be employed. In order to maintain a supply of homogenous consistency to the decantation centrifuge and to the tubular bowl centrifuge, homogenizers, such as an IKA homogenizer may be added between the separation steps. In-line homogenizers may also be added in between various centrifuges or size exclusion based separation equipment employed to wash the oil body **preparations**. Ring dam sizes, buffer **compositions**, temperature and **pH** may differ in each washing step from the ring dam size

employed in the first separation step.

DETD [0064] In embodiments of the invention where oil bodies are obtained from non-plant cells, the washed oil body **preparation** is isolated following similar procedures as outlined above. The methodology for isolating oil bodies from yeast has been documented (Ting et al., 1997, Journal Biol. Chem. 272:3699-3706).

DETD [0065] The chemical and physical properties of the oil fraction may be varied in at least two ways. Firstly, different plant species contain oil bodies with different oil **compositions**. For example, coconut is rich in lauric oils (C.sub.12), while erucic acid oils (C.sub.22) are abundantly present in some Brassica spp. Secondly, the relative amounts of oils may be modified within a particular plant species by applying breeding and genetic engineering techniques known to the skilled artisan. Both of these techniques aim at altering the relative activities of enzymes controlling the metabolic pathways involved in oil synthesis. Through the application of these techniques, seeds with a sophisticated set of different oils are obtainable. For example, breeding efforts have resulted in the development of a rapeseed with a low erucic acid content (Canola) (Bestor, T. H., 1994, Dev. Genet. 15: 458) and plant lines with oils with alterations in the position and number of double bonds, variation in fatty acid chain length and the introduction of desirable functional groups have been generated through genetic engineering (Topfer et al., 1995, Science, 268: 681-685). Using similar approaches a person skilled in the art will be able to further expand on the presently available sources of oil bodies. Variant oil **compositions** will result in variant physical and chemical properties of the oil bodies. Thus by selecting oilseeds or mixtures thereof from different species or plant lines as a source for oil bodies, or by mixing oil bodies obtained from various species or plant lines, a broad repertoire of emulsions with different textures, different properties that are beneficial to the skin and different viscosities may be acquired.

DETD [0067] The washed oil body **preparation** may be formulated into an emulsion using techniques known in the art. Preferably, at least one additional ingredient is added to the washed oil body **preparation**. The additional ingredient may be any chemical compound, including without limitation any acid or base, any organic or inorganic molecule, any ionic or non-ionic compound, any polar or non-polar molecule and any lipophilic or hydrophilic compound or, if more than one additional ingredient is added, any mixture of these compounds. The additional ingredient may be added in any desirable form, for example, the additional ingredient may be added as a solution, suspension, a gel, a crystal, a liquid or solid and the additional ingredient may be of any desirable viscosity. Quantities of the additional ingredient may be as desired and will depend on the formulation. The additional ingredient may upon formulation become associated with the oil bodies for example by the formation of non-covalent or covalent chemical bonds with the oil body, remain suspended in solution, or form a suspension in which the oil bodies are dispersed. The additional ingredient may also penetrate the phospholipid monolayer surrounding the oil body or the triacylglyceride matrix. In a further preferred embodiment the liquid phase is water. Water may be added either directly or through moisture associated with another ingredient. The final amount of water is not critical, however generally, the **compositions** will contain at least 1% of water and up to 99% water.

DETD [0070] In the course of the formulation process any type of emulsion may be formed, including without limitation an oil-in-water emulsion, a water-in-oil emulsion, a multiple (e.g. double, tri-multiple, quarter-multiple and quinque-multiple etc.) emulsion, and reverse emulsion. The **compositions** of the present invention preferably will be in the form two phases where one phase is uniformly dispersed in the other phase, and resulting in a homogenous macroscopic appearance. Where **compositions** comprising two or more non-uniformly

dispersed phases are formed they generally need to be shaken or stirred prior to application of the emulsion to the surface area of the body.

DETD [0071] The final formulation may be of any **pH**, but is preferably of a **pH** compatible with application of the emulsion to the human skin. Usually the formulation process will require mixing to provide an adequate emulsion and it may be necessary to apply heat, pressure, freezing, one or more cycles of freeze thawing or other physical forces to formulate the emulsion.

DETD [0072] The emulsion formulations for application to the surface area of the human body may comprise a wide variety of additional components and may be formulated in a wide range of products including personal care and dermatological products. The following optional ingredients and mixtures thereof represent non-limiting examples of ingredients that may be formulated with oil bodies in order to prepare a **composition** for topical application to the surface area of the human body.

DETD [0074] In a preferred embodiment of the present invention, the formulations comprising washed oil bodies are stabilized so that a formulation is obtained which may be stored for longer periods of time. For the purpose of the present application the term "stabilized oil body **preparation**" refers to a formulation comprising washed oil bodies that is prepared so that the formulation does not undergo undesirable physical or chemical reactions when the formulation is stored for longer periods of time. Preferably the oil body **preparation** is stable for at least 1 month, more preferably the **preparation** is stable for at least 1 year, and most preferably for at least 2 years when stored at room temperature. In a further preferred embodiment, the oil body **preparation** is prepared so that the **preparation** can additionally withstand temperature fluctuations such as those which typically may occur in non-temperature controlled environments, for example during transport. In accordance with the present invention generally at least one stabilization step is performed. In preferred embodiments, the oil body **preparation** is stabilized upon completion of the final washing step. However it is also possible to stabilize the oil body **preparation** prior to performing the final washing step. For example when multiple washing steps are performed, any or all of the stabilization steps may be performed prior to completion of the final washing step. In addition, any or all of the stabilizations may be performed after the addition of a further formulation ingredients.

DETD [0075] Diagnostic parameters used to assess the stability of the oil body **preparation** may be as desired and may include any and all parameters indicative of any and all qualitative or quantitative changes with respect to chemical or physical stability of the oil body **preparation**. Typical parameters used to assess alterations in the oil boy **preparation** over time include color, odor, viscosity, texture, **pH** and microbial growth. In preferred embodiments changes in the oil body **preparation** with respect to these parameters are minimal or absent.

DETD [0078] In preferred embodiments, small amounts of stabilizing chemical agents are mixed with the formulation comprising washed oil bodies in order to achieve a stable **preparation**. These chemical agents preferably constitute less than approximately 10% (w/w), more preferably less than about 5% (w/w) and most preferably less than about 2.5% (w/w) of the formulation. Chemical agents that may be used in accordance with the present invention include inter alia preservative agents; acids; bases; salts; anti-oxidants; viscosity modifying agents; emulsifiers; gelling agents; and mixtures thereof.

DETD [0083] The oil body **preparation** may be stabilized by heat treatment for example by pasteurization in a constant temperature water bath at approximately 65.degree. C. for 20 minutes. The pasteurization temperature preferably ranges from between about 50.degree. C. to about 90.degree. C. and the time for pasteurization preferably ranges from between about 10 seconds to about 35 minutes. When heat treatment techniques are used in combination with the use of chemical

preservatives, the chemical preservatives may be added prior or after the heat treatment. In embodiments where the chemical preservatives are added prior to the heat treatment these preservatives must be able to withstand the temperature regimen that is employed.

DETD [0084] In accordance with the present invention, the oil body **preparation** may also be stabilized by irradiation, for example ionizing radiation such as cobalt-60 or cesium-137 or by ultraviolet radiation.

DETD [0085] The following additional ingredients may be formulated with the stabilized oil body formulation. While in preferred embodiments of the present invention, the oil bodies are stabilized prior to the formulation with these additional ingredients, it is nevertheless possible to formulate the oil body **preparation** and stabilize the final **preparation**.

DETD [0095] Examples of amphoteric surfactants which can be used in the **compositions** of the present invention include the betaines, which can be prepared by reacting an alkyldimethyl tertiary amine, for example lauryl dimethylamine with chloroacetic acid. Betaines and betaine derivatives include higher alkyl betaine derivatives including coco dimethyl carboxymethyl betaine; sulfopropyl betaine; alkyl amido betaines; and cocoamido propyl betaine. Sulfosultaines which may be used include for example, cocoamidopropyl hydroxy sultaine. Still other amphoteric surfactants include imidazoline derivatives and include the products sold under the trade name "Miranol" described in U.S. Pat. No. 2,528,378 which is incorporated herein by reference in its entirety. Still other amphoterics include phosphates for example, cocamidopropyl PG-dimonium chloride phosphate and alkyldimethyl amine oxides.

DETD [0097] Another ingredient which may be formulated with the washed oil body emulsions of the present invention is a moisturizer. As used herein a "moisturizer" is an ingredient which promotes the retention of water to the surface area of the human body, including hair and skin. The term moisturizer as used herein includes both components which deliver water to the skin, also commonly referred to in the art as "humectant", and components which prevent the loss of water from the skin, also commonly referred to in the art as "occlusive". The moisturizer will generally comprise from about 0.1% (w/v) to about 99% (w/v), more preferably from about 0.5% (w/v) to about 50% (w/v), and most preferably from about 1% (w/v) to about 40% (w/v) of the final **composition**. Although the ingredients mentioned herein are generally defined as moisturizers they may also possess other properties such as emolliency or other conditioning properties.

DETD [0100] A further ingredient which may be formulated with the oil body **compositions** of the present invention is an emollient. Emollients typically comprise between from about 0.01% to about 25%, preferably from about 0.05% to about 15% and more preferably from about 0.1% to about 10% w/v of the total formulation. Emollients are used to add or replace lipids and natural oils to the surface area of the human body. The term emollient as used herein is intended to include conventional lipids (for example, oils, waxes, lipids and other water insoluble components) and polar lipids (lipids which have been modified in order to increase water solubility typically through esterfication of a lipid to a hydrophylic moiety for example hydroxy groups, carbonyl groups and the like). Emollients which may be used in the present invention are preferably selected from the group consisting of natural oils and preferably plant-derived and essential oils, esters, silicone oils, polyunsaturated fatty acids (PUFAs), lanoline and its derivatives and petrochemicals.

DETD [0103] Further useful emollients include silicone oils, including non-volatile and volatile silicones. Examples of silicone oils that may be used in the **compositions** of the present invention are dimethicone; cyclomethycone; dimethycone-copolyol; aminofunctional silicones; phenyl modified silicones; alkyl modified silicones; dimethyl and diethyl polysiloxane; mixed C.sub.1-C.sub.30 alkyl polysiloxane; and mixtures thereof. Additionally useful silicones are described in U.S.

Pat. No. 5,011,681 to Ciotti et al., incorporated by reference herein.

DETD [0105] Petrochemicals which may be used as emollients in the **compositions** of the present invention include mineral oil; petrolatum; isohexdecane; permethyl 101; isododecanol; C.sub.11-C.sub.12 Isoparrafin, also known as Isopar H.

DETD [0106] Among the waxes which may be included in the **compositions** of the present invention are animal waxes such as beeswax; plant waxes such as carnauba wax, candelilla wax, ouricurry wax, Japan wax or waxes from cork fibres or sugar cane. Mineral waxes, for example paraffin wax, lignite wax, microcrystalline waxes or ozokerites and synthetic waxes may also be included.

DETD [0109] A further ingredient that may be formulated with the washed oil body **compositions** in accordance with the present invention is a fragrance. Typically a fragrance comprises between about 0.0001% (v/v) and about 25% (v/v) of the final **composition**, more preferably between about 0.001% (v/v) and 10% (v/v) and most preferably between 0.01% (v/v) and 5% (v/v) of the final **composition**. For the purpose of the present application the term "fragrance" is meant to encompass any component reacting with the human olfactory sites and imparting a pleasurable odor, essence or scent. Fragrances that may be used in accordance with the present invention include any synthetic as well as natural fragrance and mixtures thereof. Typically a multiplicity of fragrances are used to achieve the desired effect. Those of skill in the art further recognize the terms "top note" (i.e. fragrances having a high vapor pressure), "middle note" (i.e. fragrance having a medium vapor pressure) and "base note" (i.e. fragrances having a low vapor pressure). Recognizing that categorization within these classes may depend to some extent on the fragrance formulator, the emulsions of the present invention may comprise any top note, middle note and base note fragrance. A further way of classifying fragrances is in accordance with generally recognized scents they produce. Descriptors used by those skilled in the art of fragrances are inter alia "rose", "floral", "green", "citrus", "spicy", "honey", "musk", "herbal", "jasmin", "lilac", "lily of the valley", "orange", "peach", "oriental", "watermelon" "chypre" and "lemon", "woody", "fruity" all of which fragrances thus classified may be formulated with the emulsions of the present invention.

DETD [0115] In accordance with the present invention a wide variety of active ingredients may be formulated with the washed oil bodies of the present invention. The terms "actives", "active agent" and "active ingredient" as used herein refers to a compound capable of enhancing or improving the physical appearance, health, fitness or performance of the surface area of the human body, including the skin, hair, scalp, teeth and nails. The amount of active formulated will depend on the desired effect and the active that is selected. In general, the amount of active varies from about 0.0001% (w/v) to about 50% (w/v). More preferably however the amount of active in the final **composition** will vary from about 0.01% (w/v) to about 20% (w/v) and most preferably from about 0.1% (w/v) to about 10% (w/v). The actives may be formulated into the washed oil body formulation in any desired manner (e.g. mixed, stirred) under any desired condition (e.g. heated; under pressure) and in any desired form (e.g. a liquid, solid, gel, crystal, suspension). Depending on the chemical nature of the active and the formulation methodology, the active may become incorporated in the final formulation in a variety of ways, for example the active ingredient may remain suspended in solution, or form a suspension in which the oil bodies are dispersed, or the active ingredients may penetrate the phospholid mono layer surrounding the oil body or the triacyl glyceride matrix of the oil body. The active also may be associated with the oil bodies. As used herein the term "associated with the oil bodies" refers to any specific interaction between the active ingredient and the oil bodies including any interaction which involves the formation of a covalent bond between the oil body and the active ingredient as well as any interaction which involves the formation of a non-covalent bond, for example an ionic

bond, between the oil body and the active ingredient. The active agent may directly associate with the oil body or indirectly via one or more intermediate molecules. As used herein "crosslinker" or "crosslinking agent" means any single molecule or plurality of inter-linked molecules capable of indirectly associating the active ingredient with the oil body. Oil bodies crosslinked to actives may comprise a plurality of covalent and non-covalent interactions or mixtures thereof. Generally the reaction to cross-link the active ingredient to the oil body will involve the oleosin protein or oil body phospholipids as reactive groups.

DETD [0127] Whitening and bleaching agents include hydroquinone and derivatives; kojic acid; lactic acid; ascorbyl acid and derivatives such as **magnesium ascorbyl phosphate**; arbutin; and licorice root. Hydroquinone and derivatives are preferred for use herein.

DETD [0164] The subject invention is directed toward the production of emulsions that are useful in topical application to the surface area of the human body, including skin, hair, teeth, nails and lips and includes personal care and dermatological products. For the purpose of the present application personal care products are meant to include all cosmetics, cosmeceuticals and beauty care products, all of which may be prepared in accordance with the present invention. Dermatological products, for the purpose of the present invention, are meant to include all products to treat or ameliorate skin conditions, abnormalities or diseases and contain one or more active ingredients capable of improving said condition, abnormality, disease. These products include any and all products that may be used to treat or ameliorate any phyiopathological conditions of the dermis or epidermis. Depending on the active ingredient which is formulated, the dermatological products of the present invention may be made available as a prescription drug or as an over-the-counter (OTC) product. It is noted that the emulsions may be applied in **compositions** which vary considerably in physical properties and use. The types and quantities of ingredients used to prepare different products will depend on the desired use of the product and may be varied in accordance with practices well known to those of ordinary skill in the art of formulating skin care and dermatological products.

DETD [0175] The dermatological **compositions** of the present invention include products which may be used to treat or reverse skin changes associated with aging such as wrinkles, blotches and atrophy or elastotic changes associated with intrinsic aging of the skin as well as changes caused by external factors for example sunlight radiation; X-ray radiation; air pollution; wind; cold; dampness; dryness; heat; smoke and cigarette smoking; external infectious agents such as fungi and bacteria; and combinations thereof.

DETD [0179] The particular product and the particular form in which the emulsion is applied, however is not of critical importance and may be as desired. It is to be clearly understood that the emulsion formulated with the washed oil body **preparation** may be applied in any product which is applied to the surface area of the human body.

DETD [0181] Obtaining a Washed Oil Body **Preparation** From Oilseed Rape, Soybean, Sunflower, White Mustard, Peanut, Squash, Flax, Safflower and Maize--Laboratory Scale.

DETD [0182] Dry mature seeds obtained from Brassica napus cv Westar, soybean, sunflower, white mustard, peanut, squash, flax, safflower and maize were homogenized in five volumes of cold grinding buffer (50 mM Tris-HCl, **pH** 7.5, 0.4 M sucrose and 0.5 M NaCl) using a polytron operating at high speed. The homogenate was centrifuged at 10.times.g for 30 minutes in order to remove particulate matter and to separate oil bodies from the aqueous phase containing the bulk of the soluble seed protein. The oil body fraction was skimmed from the surface of the supernatant with a metal spatula and added to one volume of grinding buffer. In order to achieve efficient washing in subsequent steps it was found to be necessary to thoroughly redisperse the oil bodies in the grinding

buffer. This was accomplished by gently homogenizing the oil bodies in grinding buffer using a polytron at low speed. Using a syringe, the redispersed oil bodies were carefully layered underneath five volumes of cold 50 mM Tris-HCl **pH** 7.5 and centrifuged as above. Following centrifugation, the oil bodies were removed and the washing procedure was repeated two times. The final washed oil body **preparation** was resuspended in one volume of cold Tris-HCl **pH** 7.5, redispersed with the polytron.

DETD [0185] Obtaining a Washed Oil Body **Preparation** From Oilseed Rape, Sunflower and Maize on a Large Scale.

DETD [0186] This example describes the recovery of the oil body fraction from canola, sunflower and maize seed on a large scale. The resulting **preparation** contains intact oil bodies and is comparable in purity with a **preparation** obtained using laboratory scale procedures.

DETD [0189] Oil Body Separation. Separation of the oil body fraction was achieved using a Sharples Tubular Bowl Centrifuge model AS-16 (Alpha Laval) equipped with a three phase separating bowl and removable ring dam series; capacity:150 L/hr; ringdam: 30 mm. Operating speed was at 15,000 rpm (13,200.times.g). A Watson-Marlow (Model 704) peristaltic pump was used to pump the decanted liquid phase (DL) into the tubular bowl centrifuge after bringing the centrifuge up to operating speed. This results in separation of the decanted liquid phase into a heavy phase (HP) comprising water and soluble seed proteins and a light phase (LP) comprising oil bodies. The oil body fraction which was obtained after one pass through the centrifuge is referred to as an unwashed oil body **preparation**. The oil body fraction was then passed through the centrifuge three more times. Between each pass through the centrifuge, concentrated oil bodies were mixed with approximately five volumes of fresh water. The entire procedure was carried out at room temperature. The **preparations** obtained following the second separation are all referred to as the washed oil body **preparation**. Following three washes much of the contaminating soluble protein was removed and the oil body protein profiles obtained upon SDS gel electrophoresis were similar in appearance to those obtained using laboratory scale procedures.

DETD [0190] The large scale oil body **preparation** may be pasteurized. Pasteurization is achieved by initially thickening the washed oil bodies with centrifugation to a water content of 30 to 60%, preferable between 35 and 50% weight and most preferable between 37 and 40% weight. The thickened oil body solution can then be pasteurized in a constant temperature water bath at approximately 65.degree. C. for 20 minutes. The pasteurization temperature could range between 50 and 90.degree. C. and the time for pasteurization could range between 15 seconds to 35 minutes. If the oil bodies are used in a cosmetic formulation, then before pasteurization, 0.1% Glydant Plus, 0.1% BHA and 0.1% BHT may be added as a preservative and anti-oxidants respectively.

DETD [0192] This example describes the recovery of a washed oil body fraction from canola, maize and sunflower seed. Using different washing conditions, it is shown that the washes result in the removal of significant amounts of seed proteins from the oil body **preparation**. These proteins include proteins which might be allergenic.

DETD [0193] A total of 10-15 kgs of dry canola seed (Brassica napus cv Westar), maize (Zea mays) or sunflower (Helianthus annuus) was poured through the hopper of a colloid mill (Colloid Mill, MZ-130 (Fryma)), which was equipped with a MZ-120 crosswise toothed rotor/stator grinding set and top loading hopper. Approximately 50-75l water was supplied through an externally connected hose prior to milling. Operation of the mill was at a gap setting of 1R, chosen to achieve a particle size less than 100 micron at 18.degree. C. and 30.degree. C. Following grinding of the seeds, tap water was added to the seed slurry to a final volume of 60-90 liters and a sample of the seed slurry was obtained for SDS gel electrophoresis. The slurry was then pumped into a decantation

centrifuge (Hasco 200 2-phase decantation centrifuge maximum operating speed 6,000 rpm) after bringing the centrifuge up to an operating speed of 3,500 rpm. Transfer from the mill to the decantation centrifuge was achieved using a 1 inch M2 Wilden air operated double diaphragm pump. In 15-20 minutes approximately 15 kg of seed was decanted. A sample from the decanted liquid phase was obtained for SDS gel electrophoresis. Separation of the oil body fraction was achieved using a Sharples Tubular Bowl Centrifuge model AS-16 (Alpha Laval) equipped with a three phase separating bowl and removable ring dam series; capacity: 150 L/hr; ringdam: 29 mm. Operating speed was at 15,000 rpm (13,200.times. g). A Watson-Marlowe (Model 704) peristaltic pump was used to pump the decanted liquid phase into the tubular bowl centrifuge after bringing the centrifuge up to operating speed. The unwashed oil body phase was obtained and mixed with approximately 5 volumes of water. This procedure was repeated a total of three more times. The oil body phase which was obtained following the first spin, is referred to as an unwashed oil body **preparation**. All other **preparations** are washed oil body **preparations**. Samples for analysis by SDS gel electrophoresis were obtained following the first and fourth separations.

DETD [0194] Upon completion of the fourth wash a 0.9 ml sample of the oil body **preparation** was homogenized in 0.1 ml 1 M Na.sub.2CO.sub.3 and left at room temperature for 30' with agitation. The washed oil body fraction was then recovered following centrifugation, washed once with water and prepared for SDS gel electrophoresis.

DETD [0197] A washed oil body **preparation** and an unwashed oil body phase were prepared from rapeseed as in example 2. To determine the difference in water retention capacity between the unwashed oil body phase and the washed oil body **preparation**, 30 mls of oil body **preparations** were thoroughly mixed using a vortex. The **preparations** were then incubated for 2 hours in a water bath at 40, 60 or 80.degree. C. and the samples were centrifuged at 1,500.times.g for 20 minutes (undiluted samples). Another set of samples was prepared by mixing 15 g of washed or unwashed oil body **preparation** with 15 ml of water. The samples were mixed on a vortex and then incubated at 40, 60 or 80.degree. C. for 2 hours and the amount of water present in the samples was determined following centrifugation at 1,500.times.g for 20 minutes (diluted samples). Loss of mass attributable to evaporation was measured at 80.degree. C. and 60.degree. C.

DETD [0198] At 80.degree. C., the undiluted **preparations** comprising oil bodies lost significant amounts of water through evaporation. The **preparation** of unwashed oil bodies lost 26% of their mass, while the washed **preparation** lost 16%. Upon centrifugation the unwashed **preparation** released approximately 2.5 ml of aqueous phase, while the washed oil bodies remained in the same phase. Both diluted **preparations** absorbed water. The volume of oil bodies increased in both cases to 18.5.+-.1 ml.

DETD [0199] At 60.degree. C., the undiluted **preparations** lost approximately 10% of water through evaporation. Following centrifugation, the washed **preparation** released about 0.5 ml of aqueous phase, while the washed oil body **preparation** stayed in the same phase. Both diluted **preparations** absorbed water. At 60.degree. C., the volume of oil bodies increased in both cases to 18.+-.1 ml.

DETD [0200] At 40.degree. C., the undiluted samples both released approximately 2 ml of aqueous phase. When the diluted samples were compared, the unwashed **preparation** absorbed about 3 ml of water, as was the case at 60 or 80.degree. C. However the washed **preparation** absorbed 8 ml of water at 40.degree. C.

DETD [0201] These experiments demonstrate that in a washed oil body **preparation** heated to 60.degree. C. or 80.degree. C., water remains more tightly associated with the oil body **preparation**

than in an unwashed **preparation**. When cooled down the washed oil body **preparation** appeared to be more stable than the unwashed emulsion. When heated to 40.degree. C., the washed oil body **preparation** was able to absorb a larger volume of exogenously added water without resulting in phase separation offering greater flexibility in preparing oil body based formulations.

DETD [0203] A washed oil body **preparation** and an unwashed oil body phase were prepared from rapeseed as in example 2. To determine the difference in oil absorption capacity between the unwashed oil body phase and the washed oil body **preparation**, 2 grams of the oil body **preparations** was dispersed into 12 ml of refined, bleached, deodorized canola oil in a 50 ml tube. The contents were stirred for 30 seconds every 5 minutes for 30 min. The tubes were then centrifuged at 4,400 rpm for 25 min. The free oil was decanted and the percentage of absorbed oil was determined by weight difference. Three **preparations** of washed oil bodies were tested and three **preparations** of unwashed oil bodies were tested.

DETD [0204] The oil absorption capacity of unwashed oil bodies was found to vary significantly between the three batches and varied from 18.7% to 28%. Washed oil bodies had reproducible oil absorption of 32.+-.1%. Thus the washed oil body **preparation** was found to be superior since (1) a larger amount of oil was found to be absorbed and (2) the absorption occurred in a more reproducible manner.

DETD [0205] **Preparation** of Stabilized Oil Body Emulsions Comprising Washed Safflower Oil Bodies for Use of Formulation in a Personal Care Product (Base Formulations A, B, C).

DETD [0206] A washed oil body **preparation** was prepared from safflower seeds as described in example 2. The oil bodies were transferred into a mixing pot and 0.7% keltrol was added. The mixture was then vigorously stirred at room temperature. Subsequently 2.0% glycerin was added. The mixture was then heated to 45-50.degree. C. and 0.1% butylated hydroxyanisole (BHA) and 0.1% butylated hydroxytoluene (BHT) were added. Finally 0.15% Glydant Plus was added. The procedure for Base B and C was slightly different as the temperature was subsequently increased to 60.degree. C. and 2.5% Arlacel 165 was added and mixed until a **preparation** of homogeneous appearance was obtained. The mixture was then rapidly cooled to 30.degree. C. under moderate stirring.

Base A

Hydrated safflower oil bodies (0.1% Glydant Plus, 0.1% BHT, 0.1% BHA)	96.95%
Glydant Plus	0.15%
BHT	0.1%
BHA	0.1%
Keltrol	0.7%
Glycerine	2.0%

DETD [0209] The formulations thus prepared were found to be stable with respect to color, odor, viscosity, oxidation, **pH** and microbial levels for a period of at least 3 months at 45.degree. C. The stability at 45.degree. C. can be extraolated into a stability of approximately 2 years at room temperature. The chemical analysis of the hydrated safflower oil body **preparation** revealed that the sample contained 50.82% water and 49.18% dry weight. The dry weight (DW) component consisted of 3.76% protein, 93.56% oil and 2.68% other.

DETD [0210] **Preparation** of a Cosmetically Elegant Product From Base B.

DETD [0212] **Preparation** of a Cosmetically Elegant Product From Base C.

DETD [0214] **Preparation** of a Cosmetically Elegant Product From Base

B.

DETD [0216] **Preparation** of a Sunscreen with a Sun Protection Factor of 8.

DETD [0218] **Preparation** of a Sunscreen.

DETD [0219] The water soluble ingredients Kaolin and Veegum Ultra were dissolved under moderate agitation at room temperature. The glycerin was then added. The water phase was heated to a final temperature of 75.degree. C. to 77.degree. C. and methylparaben is added. The oil phase was prepared in a separate mixing pot using moderate agitation and heated to 75.degree. C. to 77.degree. C. The oil phase ingredients that were used were Dimethicone 250, Cetyl Alcohol, Arlacel 165, Propylparaben, Safflower Oil, Trivalin SF, Palemol OL and Parsol MCX. The oil an water phases were subsequently mixed under vigorous agitation for 15 minutes. The mixture was then gradually cooled to 40.degree. C., while gradually decreasing agitation. At 40.degree. C., Germall 115 was added and when the temperature reached about 37.degree. C. to 40.degree. C. the safflower oil body **preparation** was added slowly. The mixture was allowed to cool to room temperature and the colorant (red 33 solution) was added. The final **pH** was 6.0 and viscosity was 25,000 cps.

Purified Water	47.15%
Kaolin USP	2.50%
Veegum Ultra (Mg, Al Sillicate)	5.00%
Glycerin	2.00%
Methylparaben	0.30%
Dimethicone 350	0.50%
Cetyl Alcohol	2.00%
Arlacel 165 (Glyceryl Stearate & PEG-100 Stearate)	2.50%
Propylparaben	0.15%
Safflower Oil	2.00%
Trivabn SF (Ethyoxydiglycol)	2.00%
Palemol OL (Oleyl Lactate)	1.00%
Parsol MCX (Octyl Methoxycinnamate)	7.50%
Germall 115 (Imidazolidinyl Urea)	0.30%
Hydrated Safflower Oil Body (0.1% Glydant Plus, 0.1% BHT, 0.1% BHA)	25.00%
Red #33 1%	0.10%

DETD [0220] **Preparation** of a Skin Care Cream Containing a Stable Vitamin A Derivative, Retinyl Palmitate.

DETD [0222] **Preparation** of a Day Cream.

DETD [0223] The water soluble ingredients kaolin and the Mg, Al Silicate were dissolved at room temperature. The glycerin is then added while mixing continued. The water phase was heated to a final temperature of 75.degree. C. to 77.degree. C. The oil phase was prepared in a separate mixing pot using moderate agitation and then subsequently heated up to 75.degree. C. to 77.degree. C. The oil phase ingredients that were used were Dimethicone 350, Cetyl Alcohol, Arlacel 165, Trivalin SF, and Palemol OL. The two phases were then mixed using vigorous agitation for 15 minutes. The mixture was then cooled gradually cooled to 40.degree. C. At 40.degree. C. Germaben II was added and when the temperature reached about 37.degree. C. to 40.degree. C. the safflower oil bodies were slowly added. The mixture was then allowed to cool to room temperature. The final **pH** was adjusted to 6.00 with a final viscosity of 25,060 cps.

Purified water	32.20%
Kaolin	2.50%
Veegum Ultra (Mg, Al Silicate)	5.00%
Glycerin	2.00%
Dimethicone 350	0.50%

Cetyl Alcohol	2.00%
Arlacel 165 (Glyceryl Sterate & PEG-100 Stearate)	2.50%
Trivalin SF (Ethoxydiglycol)	2.00%
Palemol OL (Oleyl Lactate)	1.00%
Germaben II (Diazolidinyl Urea)	0.30%
Hydrated Safflower Oil Body (0.1% Glydant Plus, 0.1% BHT, 0.1% BHA)	50.00%

DETD [0224] **Preparation** of a Night Cream.

DETD [0225] The water soluble ingredients Kaolin, Mg and Al Silicate were dissolved using moderate agitation at room temperature. Glycerin was added while mixing continued. The water phase was heated to a temperature of 75.degree. C. to 77.degree. C. The oil phase was prepared in a separate mixing pot using moderate agitation and heated up to 75.degree. C. to 77.degree. C. The oil phase ingredients used were Dimethicone 350, Cetyl Alcohol, Arlacel 165, Trivalin SF, and Palemol OL. The two phases were mixed under vigorous agitation for 15 minutes. The mixture was then cooled gradually to 60.degree. C. The agitation was gradually decreased as the temperature decreased. At 60.degree. C. glycolic acid was added, at 50.degree. C. a 25% solution of sodium hydroxide was added, at 40.degree. C. the Germall 115 was added and when the temperature reached about 37 to 40.degree. C. the safflower oil bodies were added slowly. The final **pH** was adjusted to 3.64 with a final viscosity of 35,000 cps.

Purified water	24.20%
Kaolin	2.50%
Veegum Ultra (Mg, Al Silicate)	5.00%
Glycerin	2.00%
Dimethicone 350	0.50%
Cetyl Alcohol	2.00%
Arlacel 165 (Glyceryl Sterate & PEG-100 Stearate)	2.50%
Trivalin SF (Ethoxydiglycol)	2.00%
Palemol OL (Oleyl Lactate)	1.00%
Glycolic Acid	8.00%
Sodium Hydroxide (25% solution)	qs **pH** 3.3-3.8
Germaben H (Diazolidinyl Urea)	0.30%
Hydrated Safflower Oil Body (0.1% Glydant Plus, 0.1% BHT, 0.1% BHA)	50.00%

DETD [0226] **Preparation** of a Facial Mask.

DETD [0228] Comparison of Washed Oil Bodies and Lipid Vesicles in the **Preparation** of Cosmetic Formulations.

DETD [0231] Table 1 summarizes the results for the oil bodies. The **pH** for the oil body sample was constant at 6.50 throughout the test at room temperature and at 45.degree. C. The oil body **preparation**, when applied to the skin, distributed evenly on the skin, was fast penetrating and left almost no residue on the skin surface. The oil body **preparation** was also stable with respect to color, odor, viscosity and emulsion stability.

DETD [0232] Table 2 summarizes the results for the lipid vesicles. The **pH** for the lipid vesicle sample is difficult to measure because of the total separation but was approximately 6.8. The lipid vesicle **preparation**, when applied to the skin, was very oily and left a film residue on the skin. The lipid vesicle **preparation** was stable with respect to microbial growth but was not stable with respect to color, odor and emulsion stability.

DETD [0233] The above results demonstrate that the oil washed oil body **preparation** is clearly superior to lipid vesicles with respect to both physical parameters (color, odor, stability) and cosmetic parameters (penetration, residual residue, and oiliness). These parameters are critical to the **preparation** of personal care products.

DETD [0234] **Preparation** of Body Wash Formulations.

DETD [0235] Washed safflower oil bodies were prepared as described in Example 2. Following the final wash step, 0.2% (w/v) Glydant Plus was added. The washed oil bodies comprising Glydant Plus were then pasteurized using a plate and frame pasteurizer at 72.degree. C. for 16 seconds and cooled to room temperature. The pasteurized oil body **preparation** was then heated to 60.degree. C. in a hot water bath and 2.5% (w/v) previously melted Arlacel 165 was added. The sample was removed from the hot water bath and 0.7% (w/v) Keltrol CG and 2% (w/v) glycerol were added. The sample was then allowed to cool to 50.degree. C. and put on ice to cool to 25.degree. C. 0.1% (v/v) phytic acid was added and the **pH** was set at 6.5 using a solution of 50% (w/v) of NaOH. The oil body **preparation** thus obtained is a stabilized oil body **preparation** and was used to prepare the formulations further described below and in Examples 18-20.

Stabilized Oil Bodies

Safflower oilbodies	96.50
Keltrol CG	0.70
Arlacel 165	2.50
Phytic acid	0.10
Glydant plus	0.20

DETD [0240] **Preparation** of a Liquid Formulation for Hand or Hair Washing. Stabilized oil bodies were prepared as described in Example 17 and used for the **preparation** of a handwash or shampoo formulation as follows:

Hand Washing Liquid or Shampoo

Miracare BT	5.00
Lauramide DEA	3.00
Glycerine	2.00
Na.sub.2EDTA	0.05
Stabilized oil bodies	25.0
TEA Lauryl Sulfate	30.0
Water, fragrance	qs
Viscosity, cps	5000

DETD [0242] **Preparation** of a Conditioning Shampoo. Stabilized oil bodies were prepared as described in Example 17 and used for the **preparation** of a conditioning shampoo formulation as follows:

Miracare BT	5.00
Lauramide DEA	3.00
Glycerine	2.00
Na.sub.2EDTA	0.05
Carbomer	0.6
Polysorbate 20	0.5
Glydant Plus	0.1
Stabilized oil bodies	10.0
TEA Lauryl Sulfate	30.0
Water, fragrance	Qs
Viscosity, cps	7500

DETD [0243] **Preparation** of a Hand Wash Stabilized oil bodies were prepared as described in Example 17 and used for the **preparation** of an antimicrobial handwash formulation as follows:

Anti-microbial hand wash

Cetyl Hydroxyethyl Cellulose	1.00
Lauramide DEA	3.00
Cocoamidopropyl betaine	10.0
Na.sub.2EDTA	0.05
Sodium Laureth sulfate, 70%	15.0
SOB#1030 Primary Ingredient	25.0
Irgasan DP 300	0.2
Water, fragrance	Qs
Viscosity, cps	5000

CLM What is claimed is:

35. A method for preparing an emulsion formulation for topical application comprising: (1) obtaining oil bodies from a cell; (2) washing the oil bodies to obtain a washed oil body **preparation** ; and (3) formulating the washed oil body **preparation** with a preservative agent into an emulsion for use in a product for topical application.

39. A method according to claim 35 wherein the washed oil body **preparation** comprises substantially intact oil bodies.

40. A method for preparing an emulsion formulation for topical application comprising: (1) obtaining oil bodies from plant seeds by a method that comprises: grinding plant seeds to obtain ground seeds comprising substantially intact oil bodies; removing solids from the ground seeds; and separating the oil body phase from the aqueous phase; (2) washing the oil body phase to yield a washed oil body **preparation**; and (3) formulating the washed oil body **preparation** with a preservative agent into an emulsion for use in a product for topical application.

41. A method according to claim 40 wherein said washed oil body **preparation** comprises less than about 75% (w/w) of the endogenously present non-oil body seed proteins.

42. A method according to claim 40 wherein said washed oil body **preparation** comprises less than about 50% (w/w) of the endogenously present non-oil body seed proteins.

43. A method according to claim 40 wherein said washed oil body **preparation** comprises less than about 20% (w/w) of the endogenously present non-oil body seed proteins.

44. A method according to claim 40 wherein said washed oil body **preparation** comprises less than about 10% (w/w) of the endogenously present non-oil body seed proteins.

IT 50-21-5, Lactic acid, biological studies 50-81-7, Vitamin C, biological studies 56-81-5, Glycerol, biological studies 58-95-7, Tocopherol acetate 68-26-8, Vitamin A 69-72-7, Salicylic acid, biological studies 79-14-1, Glycolic acid, biological studies 79-81-2, Retinyl palmitate 83-86-3, Phytic acid 94-13-3, Propylparaben 94-36-0, Benzoyl peroxide, biological studies 99-76-3, Methylparaben 111-90-0, Trivalin SF 120-40-1, Lauramide DEA **123-31-9**, Hydroquinone, biological studies 128-37-0, Butylated hydroxytoluene, biological studies 131-57-7, Benzophenone-3 139-33-3, Disodium EDTA 139-96-8, TEA lauryl sulfate 150-13-0, p-Aminobenzoic acid 151-21-3, Sodium lauryl sulfate, biological studies 1314-13-2, Zinc oxide, biological studies 1332-37-2, Iron oxide, biological studies 1340-68-7, Bentone 1406-16-2, Vitamin D 1406-18-4, Vitamin E 2235-54-3, Ammonium Lauryl sulfate 2682-20-4, Neolone 3380-34-5, Triclosan 5466-77-3, Octyl p-methoxycinnamate 7681-57-4, Sodium metabisulfite 8066-38-4, Phenonip 9000-07-1, Carrageenan 9000-40-2, Carob gum 9001-62-1,

Lipase 9001-92-7, Protease 9004-34-6, Cellulose, biological studies 9004-82-4, Sodium Lauryl ether sulfate 9005-64-5, Polysorbate 20 9006-65-9, Dimethicone 350 9013-79-0, Esterase 9033-06-1, Glucosidase 9035-73-8, Oxidase 9037-80-3, Reductase 11138-66-2, Keltrol CG 12001-79-5, Vitamin K 13463-67-7, Titanium dioxide, biological studies 18472-51-0, Chlorhexidine gluconate 25013-16-5, Butylated hydroxyanisole 25322-68-3, Polyethylene glycol 27503-81-7, 2-Phenylbenzimidazole-5-sulfonic acid 36653-82-4, Cetyl alcohol 39236-46-9, Germall 115 39464-87-4, Sclerogum 42175-36-0 55127-92-9, Vitamin Q 55965-84-9, Kathon 67167-59-3, Polyethylene glycol stearate 70356-09-1, Butylmethoxydibenzoylmethane 74565-11-0, Finsolv TN 84517-95-3, Germaben II 84750-06-1, Arlacel 165 107282-91-7, Euxyl 100 125018-88-4, Glydant Plus 223717-75-7 445290-06-2, Miracare BT
(products for topical applications comprising oil bodies)

ACCESSION NUMBER: 2002:198244 USPATFULL
TITLE: Products for topical applications comprising oil bodies
INVENTOR(S): Deckers, Harm M., Calgary, CANADA
Van Rooijen, Gijs, Calgary, CANADA
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Goll, Janis, Calgary, CANADA
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002106337	A1	20020808
APPLICATION INFO.:	US 2001-983546	A1	20011024 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-577147, filed on 24 May 2000, PATENTED Continuation-in-part of Ser. No. US 1999-448600, filed on 24 Nov 1999, PATENTED Continuation-in-part of Ser. No. US 1998-84777, filed on 27 May 1998, PATENTED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-75863P	19980225 (60)
	US 1998-75864P	19980225 (60)
	US 1997-47779P	19970528 (60)
	US 1997-47753P	19970527 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MICHELINE GRAVELLE, Bereskin & Parr, 40 King Street West, Box 401, Toronto, ON, M5H 3Y2
NUMBER OF CLAIMS: 49
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 2449
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L72 ANSWER 6 OF 10 USPATFULL
SUMM [0020] In another embodiment, the present invention involves a topical skin exfoliation **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid. It may further comprise hydroquinone. In one embodiment, the **composition** is 16-14 parts L+lactic acid, 18-24 parts citric acid, 2 parts kojic acid and 50 to 65 parts ethyl alcohol. A preferred topical skin exfoliation **composition** useful in skin peels involves 10-16 parts L+lactic acid, 12-18 parts citric acid, 14 parts salicylic acid, 2 parts kojic acid and 50 to 65 parts ethyl alcohol.

SUMM [0022] a) obtaining a **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid;

SUMM [0023] b) applying a coating of said **composition** to the facial skin in an amount effective to cause skin peeling.

SUMM [0025] a) prior to applying said **composition**, thoroughly cleansing facial skin to be exfoliated using an appropriate degreaser;

SUMM [0026] b) applying a second coat of said **composition** to the facial skin 2 to 4 minutes after the first coat;

SUMM [0027] c) applying third and further coats of said **composition** to the facial skin at 2 to 4 minute intervals until appearance of crystals or "frosting";

SUMM [0031] None before have prepared a **composition** according to the present invention for the use of a superior skin exfoliation or peeling **composition**. Of course, neither has such **composition** been used in a method for such a procedure.

DETD [0039] Glycolic acid has the smallest molecule of the alpha hydroxy acids allowing for enhanced penetration into the dermal layers when conditions warrant. It is commercially available as a white crystalline compound that is 99% pure and also as a 70% aqueous solution. Preferred embodiments include addition of kojic acid and derivatives thereof along with additional components such as hydroquinone in the 1 to 2% range. Skin response to glycolic acid depends not only on its concentration and **pH** but also on other factors such as the amount of free acid delivered to the skin, the duration of contact, **preparation** of the skin before peeling, and the condition of the skin before treatment.

DETD [0067] The effect of the skin peeling treatment with and without hydroquinone was tested by comparative application of the method. In this example the subjects were directed to wash both arms with cleanser, consisting of acetone. The arms were then cleaned with a balancing toner. Then, four successive coats of the skin peeling **composition**, consisting of Example 3 were applied. Subjects were then directed to wipe off the dried film with more toner and to apply sunscreen to protect the treated skin. This was followed by a twice-daily regiment of wash, toner, and sunscreen.

DETD [0071] All of the **compositions** and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the **compositions** and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the **compositions** and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

CLM What is claimed is:

19. A topical skin exfoliation **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid.

20. The **composition** of claim 19, defined further as consisting of 16 to 24 parts L(_) lactic acid, 18 to 24 parts citric acid, 2 parts kojic acid, and 50 to 65 parts ethyl alcohol.

21. The **composition** of claim 19, defined further as comprising hydroquinone.

22. A topical skin exfoliation **composition** comprising 10 to 16 parts L(+) lactic acid, 12 to 18 parts citric acid, 14 parts salicylic

acid, 2 parts kojic acid, and 50 to 65 parts ethyl alcohol.

23. A method for facial exfoliation, comprising the following steps: a) obtaining a **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid; b) applying a coating of said **composition** to the facial skin in an amount effective to cause skin peeling.

24. The method of claim 23, further comprising: a) prior to applying said **composition**, thoroughly cleansing facial skin to be exfoliated using an appropriate degreaser; b) applying a second coat of said **composition** to the facial skin 2 to 4 minutes after the first coat; c) applying third and further coats of said **composition** to the facial skin at 2 to 4 minute intervals until appearance of crystals or "frosting"; d) cleaning the facial skin with a water dampened sponge or equivalent; e) applying hydrator mixture comprising octylmethoxy cinnaminate, benzophenone 3 and titanium dioxide in aloe vera solution the first night after peel; and f) performing additional treatments at biweekly or monthly intervals until desired results are obtained.

IT 50-81-7, Ascorbic acid, biological studies 51-85-4, Cystamine 52-90-4, L-Cysteine, biological studies 53-86-1, Indomethacin 56-87-1, L-Lysine, biological studies 57-13-6, Urea, biological studies 60-33-3, Linoleic acid, biological studies 64-17-5, Ethanol, biological studies 69-72-7, Salicylic acid, biological studies 74-79-3, L-Arginine, biological studies 77-92-9, Citric acid, biological studies 79-09-4, Propionic acid, biological studies 98-92-0, Niacinamide 103-85-5, Phenylthiourea 108-46-3, Resorcinol, biological studies 108-95-2, Phenol, biological studies 119-61-9, Benzophenone, biological studies **123-31-9**, Hydroquinone, biological studies 123-99-9, Azelaic acid, biological studies 302-79-4, Retinoic acid 331-39-5, Caffeic acid 461-72-3, Hydantoin 471-53-4, Glycyrrhetinic acid 476-66-4, Ellagic acid 491-38-3D, Chromone, derivs. 497-76-7, Arbutin 501-30-4D, Kojic acid, succinimide ester 621-82-9, Cinnamic acid, biological studies 1135-24-6, Ferulic acid 1182-34-9, Dicaffeoylquinic acid 1197-18-8, Tranexamic acid 1405-86-3, Glycyrrhizic acid 3131-52-0, 5,6-Dihydroxyindole 3416-24-8, Glucosamine 5072-26-4, Buthionine sulfoximine 5466-77-3, Octyl p-methoxycinnamate 7704-34-9, Sulfur, biological studies 9012-76-4, Chitosan 9054-89-1, Superoxide dismutase 9083-38-9, Melanostatin 12001-79-5, Vitamin K 13463-67-7, Titania, biological studies 15431-40-0, Magnesium ascorbate 25104-18-1, Polylysine 25138-66-3, S-Lactoylglutathione 27025-41-8, Oxidized glutathione 38000-06-5, Polylysine 56328-22-4 61230-27-1, Feldamycin **108910-78-7** 124134-09-4 154160-11-9
(.alpha.-hydroxy acid-kojic acid skin peel)

ACCESSION NUMBER: 2002:157685 USPATFULL
TITLE: Hydroxy-kojic acid skin peel
INVENTOR(S): Ancira, Margaret M., Scottsdale, AZ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002082293	A1	20020627
APPLICATION INFO.:	US 2001-974743	A1	20011009 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-299788, filed on 22 Feb 1999, GRANTED, Pat. No. US 6300369 Continuation of Ser. No. US 1997-795231, filed on 10 Feb 1997, GRANTED, Pat. No. US 5874463 Continuation-in-part of Ser. No. US 1994-328006, filed on 24 Oct 1994, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Robert E. Hanson, FULBRIGHT & JAWORSKI L.L.P., Suite

2400, 600 Congress Avenue, Austin, TX, 78701
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L72 ANSWER 7 OF 10 USPATFULL

AB This invention comprises administering to a human or animal in need of treatment an effective amount of an antioxidant lipoic acid derivative and/or pharmaceutically acceptable salts and solvates thereof for the treatment or prevention of pathological (inflammatory, proliferative and degenerative diseases, e.g. diabetes mellitus, atherosclerosis, Alzheimer's disease and chronic viral diseases) and non-pathological (e.g. skin aging and wrinkle formation) conditions caused by oxidative damage. Methods of synthesizing novel antioxidant lipoic acid derivatives and their use in preventing or treating diseases or conditions caused by oxidative stress and other free radical mediated conditions are described. Another aspect of this invention is the use of these antioxidant **compositions** for the protection of skin from damage caused by ultraviolet radiation and dessication, and to provide improved skin feel by desquamating, cleansing and clarifying the skin. The **compositions** described in this invention increase cellular viability of epidermal cells, promote cytoprotection, and decrease the production of inflammatory mediators such as inflammatory cytokines in these cells. The antioxidant **compositions** are incorporated into sunscreen products, soap, moisturizing lotions, skin toners, and other skin care products.

SUMM [0014] **Compositions** that incorporate Vitamins A or E, or their derivatives, in sunscreen **compositions**, are shown in U.S. Pat. Nos. 4,454,112; 5,532,805; and 5,378,461. The use of Vitamin C in combination with Vitamins A, E, B and other agents in a skin protectant **composition**, is described in U.S. Pat. No. 4,938,960. An antioxidant **preparation** that is said to protect the skin against harmful ultraviolet radiation is disclosed in U.S. Pat. No. 5,607,921, and contains Vitamin C, in combination with Vitamins A and E, and monosaccharide or amide precursors. Sunscreen **compositions** containing panthenol and other agents are disclosed in U.S. Pat. Nos. RE 33,845; 5,505,935; 5,445,823; and 5,573,754. The antioxidant effect of superoxide dismutase when externally applied to the skin to protect against the effects of ultraviolet radiation is also described in U.S. Pat. No. 5,601,806.

SUMM [0015] In spite of advances in recent years in the protection of skin from harmful ultraviolet radiation, the epidemic of skin cancer and skin damage from the effects of this radiation has continued unabated. The loss of portions of the ozone layer from environmental pollution is believed to have contributed to an increase in ambient ultraviolet radiation that reaches exposed skin. Many skin protection **preparations** that could prevent sun damage have an unacceptable odor or texture that discourages their more frequent use, and many of the available skin protectants do not sufficiently protect the skin from these many mechanisms of injury. Hence there is a significant public health need for commercially acceptable or improved **preparations** that can be topically applied to human and animal skin, to offset the harmful effects of ultraviolet radiation.

SUMM [0016] It is therefore an object of the invention to provide a therapeutic or cosmetic **composition** containing new antioxidants, or agents that reduce sun induced skin damage and inflammation by aborting the production of inflammatory mediators and production of ROS in the skin.

SUMM [0017] It is another object of the invention to provide such a

composition having a superior therapeutic or cosmetic effect. Yet another object is to provide such **compositions** that have characteristics that will encourage their use.

SUMM [0018] The present invention relates to pharmaceutical **compositions** or salts and solvates thereof, containing isolipoic acid, R-.alpha.-lipoic acid, S-.alpha.-lipoic or their derivatives, as an active ingredient. The **compositions** are useful because they inhibit, for example, inflammatory and proliferative processes, and oppose or ameliorate the oxidative stress imposed on organismal physiological processes, including the mediation of cytoprotective effects on cells, resulting in improved cell health and survival. Another aspect of this invention extends to metabolites of .alpha.-lipoic acid, including but not limited to 3-keto-lipoic acid, racemic dihydrolipoic acid, racemic lipoamide, and their optical isomers, R and S optical isomers.

SUMM [0020] Therefore, one aspect of the present invention provide improved pharmaceutical **compositions** which have, in particular, analgesic and anti-inflammatory activity. The invention relates to pharmaceutical **compositions** containing as active ingredient either R-.alpha.-lipoic acid or S-.alpha.-lipoic acid (i.e. the optical isomers of .alpha.-lipoic acid or derivatives thereof) or isolipoic acid or derivatives thereof, or a pharmaceutically acceptable salt of these compounds, their **preparation** and their use for the **preparation** of appropriate pharmaceutical and cosmeceutical **compositions**. These are particularly suitable for combating pain and inflammation. In another aspect of this invention, a cytoprotective activity is also obtained.

SUMM [0022] This invention comprises the synthesis of novel synthetic lipoic acid derivatives and **compositions** thereof, and their use cosmetic, nutritional and pharmaceutical uses. The subject invention relates to **compositions** for oral, intravenous, intradermal, subcutaneous, intramuscular or topical application. Oral delivery is the preferred method of administration for most nutritional and pharmaceutical uses. For example, compounds described in this invention are administered orally as are anti-oxidant vitamins (e.g. vitamin C or vitamin E) or vitamin-like substances (e.g. flavonoids such flavones, isoflavones and polyphenols). In another aspect, these pharmaceutical **compositions** have a cytoprotective activity and are suitable for combating pain and inflammation.

SUMM [0024] In another aspect of this invention, these **compositions** are also useful for conditioning desquamating, and cleansing the skin and for relieving dry skin. These **compositions** can be in the form of leave-on products or products that are rinsed or wiped from the skin after use. The **composition** contains certain active ingredients including at least one cyclic polyanionic polyols, and/or at least one zwitterionic surfactant. Topical, intradermal, subcutaneous, intramuscular delivery are preferred methods of administration for most cosmetic uses, including their use in preventing skin aging and wrinkle formation, improving skin turgor and elasticity, improving or eliminating wrinkles, and improving the feel and visual appearance of skin, especially human facial skin. In a particular embodiment, the **composition** includes an antioxidant lipoic acid derivative in combination with other antioxidant species such as panthenol, grape seed extract, vitamin C, vitamin E, vitamin A or other retinoid, and superoxide dismutase, which exhibit a synergistic effect in protecting the skin from the adverse effects of dessication, aging and ultraviolet radiation.

SUMM [0025] The **compositions** of the present invention are useful for topical application to human skin and for systemic (oral) use in

mammals, including humans. The preferred method of delivery is topical application to the skin. These **compositions** provide improved skin feel, and can be in the form of leave-on products or products that are rinsed or wiped from the skin after use. These **compositions** are also useful for conditioning the skin, for desquamating the skin, for cleansing and clarifying the skin, for reducing skin pore size, and also for relieving dry skin.

SUMM [0027] Skin problems such as dry skin, psoriasis, ichthyosis, dandruff, acne, callus, photodamaged skin, aged skin, and sunburn can be described as disorders of keratinization in which the shedding of stratum comeum cells at the skin surface is altered relative to normal, young, healthy skin. Such alteration results in shedding of large clusters of cells leading to visible scaling of the skin, a build-up of keratinaceous material on the surface or in follicles or ducts, and a rough texture to the skin surface. These conditions can be improved by removal of the outermost keratinaceous material. In other words, by desquamation. Additionally there is an ongoing need to effectively deliver a wide variety of active ingredients to the skin, either via direct application of such a **composition**, or in the case of a cleansing **composition**, via the cleansing process.

SUMM [0028] Therefore, there is a need for topical skin care **compositions** which give the skin a smooth and elegant skin feel, which are useful for treating dry skin, and which are useful for providing a desquamation benefit. There is also a need for providing cleansing products have these attributes. There is also a need for **composition** which are also useful for delivering a wide variety of active ingredients to the skin, either directly to the skin or during the cleansing process.

SUMM [0029] In the present invention skin care **compositions** containing a combination of amphoteric surfactants, anionic surfactants, and cationic surfactants are useful for providing these skin care benefits. It is therefore an object of the present invention to provide skin care **compositions** for topical application to the skin. It is another object of the present invention to provide skin care **compositions** having improved skin conditioning properties, and which are also mild and nonirritating to the skin.

SUMM [0030] It is another object of the present invention to provide skin care **compositions** which improve skin dryness and which give the skin a smooth, soft, silky feel.

SUMM [0031] It is another object of the present invention to provide skin care **compositions** which are useful delivering a wide variety of active ingredients to the skin.

SUMM [0032] It is another object of the present invention to provide skin care **compositions**, which, when in the form of cleansing **compositions**, are useful for delivering a wide variety of active ingredients to the skin via the cleansing process.

SUMM [0036] This invention comprises the synthesis of novel synthetic lipoic acid derivatives and **compositions** thereof, and their use cosmetic, nutritional and pharmaceutical uses. The subject invention relates to **compositions** for oral, intravenous, intradermal, subcutaneous, intramuscular or topical application. Oral delivery is the preferred method of administration for most nutritional and pharmaceutical uses. For example, compounds described in this invention are administered orally as are anti-oxidant vitamins (e.g. vitamin C or vitamin E) or vitamin-like substances (e.g. flavonoids such flavones, isoflavones and polyphenols). Topical, intradermal, subcutaneous, intramuscular delivery are preferred methods of administration for most

cosmetic uses, including their use in preventing skin aging and wrinkle formation, improving skin turgor and elasticity, improving or eliminating wrinkles, and improving the feel and visual appearance of skin, especially human facial skin.

SUMM [0037] In another aspect of this invention, these **compositions** are also useful for conditioning desquamating, and cleansing the skin and for relieving dry skin. These **compositions** can be in the form of leave-on products or products that are rinsed or wiped from the skin after use. The **composition** contains certain active ingredients including at least one cyclic polyanionic polyols, and/or at least one zwitterionic surfactant. In another aspect, these pharmaceutical **compositions** have a cytoprotective activity and are suitable for combating pain and inflammation.

SUMM [0041] For ophthalmic applications (Table VII), the therapeutic compound is formulated into solutions, suspensions, and ointments appropriate for use in the eye. The concentrations are usually as discussed above for topico-local **preparations**. For ophthalmic formulations, see Mitra (ed.), Ophthalmic Drug Delivery Systems, Marcel Dekker, Inc., New York, N.Y. (1993) and also Havener, W. H., Ocular Pharmacology, C. V. Mosby Co., St. Louis (1983). The therapeutic compound is alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal **preparation** or solid particles containing the compound. A nonaqueous (e.g., fluorocarbon propellent) suspension could be used. Sonic nebulizers are preferred because they minimize exposing the therapeutic compound to shear, which can result in degradation of the compound.

SUMM [0043] For oral administration, either solid or fluid unit dosage forms can be prepared. For preparing solid **compositions** such as tablets, the compound of interest is mixed into formulations with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar materials as pharmaceutical diluents or carriers. Capsules are prepared by mixing the compound of interest with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compound of interest with an acceptable vegetable oil, light liquid petrolatum or other inert oil. Fluid unit dosage forms for oral administration such as syrups, elixirs and suspensions can be prepared. The water soluble forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic (e.g., ethanol) vehicle with suitable sweeteners such as sugar and saccharin, together with an aromatic flavoring agent. Suspensions can be prepared with an aqueous vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

SUMM [0044] Slow or extended-release delivery systems, including any of a number of biopolymers (biological-based systems), systems employing liposomes, and polymeric delivery systems, can be utilized with the **compositions** described herein to provide a continuous or long term source of therapeutic compound. Such slow release systems are applicable to formulations for topical, ophthalmic, oral, and parenteral use.

SUMM [0050] The daily dose of a lipoic acid derivative in humans should for example be between 70-80 mg per kg weight; the single dose for example 16-20 mg per kg body weight, this dose appropriately being given 4 times daily: the pharmaceutical **compositions** therefore preferably contain 1-1.5 g of the lipoic acid derivative in a pharmaceutical formulation, a dose of this type preferably being given 4 times each

day.

SUMM [0053] For the treatment of disorders caused by retroviruses, in particular HIV viruses, appropriate pharmaceutical **compositions** should contain such an amount of R- or S-lipoic acid or a lipoic acid derivative, this should be administered in such an amount, that single or repeated application achieves in the body a level of activity between 3.5 and 200 mg/kg, preferably 7 and 100 mg, in particular between 35 and 70 mg/kg body weight.

SUMM [0058] For example the preferred daily dose of lipoic acid or lipoic acid derivative is preferably 80 mg for the parenteral form of application and 200 mg for the oral form dosed once or twice daily. In particular, the daily dose for the parenteral form of application is 100 mg or 200 mg for the oral form. The pharmaceutical **compositions** are preferably administered orally but may also be administered parenterally (intravenously, intraarticularly, intramuscularly, subcutaneously, intradermally), or delivered or applied in the form of a solution, suspension, gel, lotion, ointment or other suitable delivery vehicle topically, directly to the skin, intraorally, sublingually, as an inhalation, or per rectum, or per vagina directly applied or as a suppository.

SUMM [0059] Pharmaceutical **compositions** containing compounds described in this invention as active ingredient may for example be formulated in the form of tablets, capsules, pills or coated tablets, granulates, pellets, plasters, solutions or emulsions, the active ingredient in each case optionally being combined with appropriate auxiliary and carrier substances. In the case of solutions, these contain for example 0.5 to 20% by weight, preferably 1 to 10% by weight of one of the optical isomers of .alpha.-lipoic acid (in each case either the iso-form or R-form or S-form or derivative thereof).

SUMM [0060] The dosage unit of the pharmaceutical **composition** with the optical isomers of .alpha.-lipoic acid or a therapeutically useful salt thereof (in each case either the R-form or the S-form) may, for example, contain:

SUMM **COMPOSITIONS**/FORMULATIONS FOR TOPICAL ADMINISTRATION

SUMM [0067] The **compositions** of the present invention are useful for application to human skin. These **compositions** are useful for conditioning the skin, for desquamating the skin, for treating dry skin, for delivering active ingredients to the skin, and in the cleansing embodiments, for cleansing the skin without over-drying or irritating the skin.

SUMM [0068] Without being limited by theory it is believed that the amphoteric surfactant of these **compositions** can potentially complex with both the anionic and cationic surfactant components. Additionally, the anionic surfactant can potentially complex with the cationic surfactant component. These multiple complexes tend to be viscous and lubricious leading to a soft or smooth, elegant skin feel. These complexes are also believed to be highly stable relative to the individual surfactant components. These complexes are useful for aiding in the delivery to the skin of any active ingredients which can be present in the **compositions**. In the case of a cleansing **composition**, these complexes tend to deposit out from the **composition**, thereby helping to carry any active ingredients to the skin's surface, while leaving a soft, smooth skin feel. Because the postulated complexes can contain various combinations of amphoteric, anionic, and cationic surfactants, these complexes are also effective for cleansing the skin and for promoting the desquamation process. Because the charges on the individual surfactants are complexed, the

surfactants are tendered less harsh and irritating to the skin versus the free surfactants.

SUMM [0069] The **compositions** of the present invention can be formulated into a wide variety of product types including, but not limited to creams, lotions, mousses, sprays, "rinse-off" cleansers, "water-less" cleansers, bars, gels, and the like. The term "rinse", as used herein, means that the **composition** is in a form that can be used in a cleansing process whereby the **composition** is ultimately rinsed or washed from the skin with water to complete the cleansing process. The term "water-less", as used herein, means that the **composition** is in the form that can be used in a cleansing process without water whereby the **composition** is typically removed by wiping with a device such as a cotton ball, a cotton pad, a tissue, a towel, and the like.

SUMM [0070] The term "pharmaceutically-acceptable," as used herein, means that the **compositions** and components thereof so described are of sufficiently high purity and are suitable for use in contact with human skin and tissues without undue toxicity, irritation, incompatibility, instability, allergic response, and the like.

SUMM [0073] The **composition** of the present invention comprise from about 0.1% to about 20%, more preferably from about 0.2% to about 10%, and most preferably from about 0.5% to about 5% of an amphoteric surfactant. The term "amphoteric surfactant," as used herein, is also intended to encompass zwitterionic surfactants, which are well known to formulators skilled in the art as a subset of amphoteric surfactants.

SUMM [0074] A wide variety of amphoteric surfactants can be used in the **compositions** of the present invention. Particularly useful are those which are broadly described as derivatives of aliphatic secondary and tertiary amines, preferably wherein the nitrogen is in a cationic state, in which the aliphatic radicals can be straight or branched chain and wherein one of the radical contains an ionizable water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. Nonlimiting examples of amphoteric surfactant useful in the **compositions** of the present invention are disclosed in McCutcheon's, Detergents and Emulsifiers, North American edition (1986), published by allured Publishing Corporation; and McCutcheon's, Functional Materials, North American Edition (1992); both of which are incorporated by reference herein in their entirety.

SUMM [0079] The **compositions** of the present invention comprise from about 0.1 % to about 20%, more preferably from about 0.2% to about 10%, and most preferably from about 0.5% to about 5% of an anionic surfactant. Nonlimiting examples of anionic surfactants useful in the **compositions** of the present invention are disclosed in McCutcheon's, Detergents and Emulsifiers, North American edition (1986), published by allured Publishing Corporation; McCutcheon's, Functional Materials, North American Edition (1992); and U.S. Pat. No. 3,929,678, to Laughlin et al., issued Dec. 30, 1975 all of which are incorporated by reference herein in their entirety.

SUMM [0085] The **compositions** of the present invention comprise from about 0.1 % to about 15%, more preferably from about 0.2% to about 10%, and most preferably from about 0.5% to about 5% of a cationic surfactant. Nonlimiting examples of cationic surfactants useful in the **compositions** of the present invention are disclosed in McCutcheon's, Detergents and Emulsifiers, North American edition (1986), published by allured Publishing Corporation; and McCutcheon's, Functional Materials, North American Edition (1992); both of which are incorporated by reference herein in their entirety. Nonlimiting examples of cationic surfactants useful herein include cationic ammonium salts

according to the teaching of U.S. Pat. No. 5,607,980 Mar. 4, 1997 and U.S. Pat. No. 5,821,237 Oct. 13, 1998, incorporated by reference herein.

SUMM [0091] The **compositions** of the present invention comprise from about 45% to about 99.7%, more preferably from about 60% to about 95%, and most preferably from about 70% to about 90% of water. The exact level of water will depend upon the form of the product and the desired moisture content.

SUMM [0093] The **compositions** of the present invention can comprise a wide range of additional components. The CTFA Cosmetic Ingredient Handbook, Second Edition, 1992, which is incorporated by reference herein in its entirety, describes a wide variety of cosmetic and pharmaceutical ingredients commonly used in the skin care industry, which are suitable for use in the **compositions** of the present invention. Nonlimiting examples of functional classes of ingredients are described at page 537 of this reference. Examples of these functional classes include: absorbents, abrasives, anti-acne agents, anticaking agents, antifoaming agents, antimicrobial agents, antioxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, external analgesics, film formers, fragrance comoponents, humectants, opacifying agents, **pH** adjusters, plasticers, preservatives, propellants, reducing agents, skin bleaching agents, skin-conditioning agents (emollient, humectants, miscellaneous, and occlusive), skin protectants, solvents, foam boosters, hydrotropes, solubilizing agents, suspending agents (nonsurfactant), sunscreen agents, ultraviolet light absorbers, and viscosity increasing agents (aqueous and nonaqueous). Examples of other functional classes of materials useful herein that are well known to one of ordinary skill in the art include emulsifiers, sequestrants, skin sensates, and the like.

SUMM [0094] Nonlimiting examples of these additional components cited in the CTFA Cosmetic Ingredient Handbook, as well as other materials useful herein, include the following: vitamins and derivatives thereof [e.g., vitamin C, Vitamin A (i.e. retinoic acid), retinol, esters of retinoic acid, esters of retinol, retinoids, pathenol, pathenol esters, tocopherol, tocopherol esters, phytic acid, phytic acid esters, lycopene, flavones, flavononones, isoflavones, flavonols and other flavonoids]; oil or sebum control agents such as clays silicones and drug actives; sunscreening agents; other silicone material such as dimethiconol, dimethicone copolyol, and amodimethicone, and the like; anti-oxidants; anti-microbial agents; preservatives; emulsifiers; polyethylene glycols and polypropylene glycols; polymers for aiding the film-forming properties and substantivity of the **compositions** (such as a copolymer of eicosene and vinyl pyrrolidone, an example of which is available from GAF Chemical Corporation as Ganex.RTM. V-220); preservatives for maintaining the antimicrobial integrity of the **compositions**; anti-acne medicaments (e.g., resorcinol, sulfur, salicylic acid, erythromycin, zinc, and the like); skin bleaching (or lightening) agents including but not limited to hydroquinone, kojic acid; antioxidants; chelators and sequestrants; thickening agents such as carbomers (homopolymers of acrylic acid crosslinked with an allyl ether of pentaerythritol or an ally ether of sucrose), crosslinked and noncrosslinked nonionic and cationic polyacrylamides [e.g., Salcare.RTM. SC92 which has the CTFA designation polyquaternium 32 (and) mineral oil, and Salcare.RTM. SC95 which has the CTFA designation polyquaternium 37 (and) mineral oil (and) PPG-1 trideceth-6, and the nonionic Seppi-Gel polyacrylamides available from Seppic Corp.]; proteins and peptides; enzymes; ceramides; aesthetic components such as fragrances, pigments, colorings, essential oils, skin senates, astringents, skin soothing agents, skin healing agents and the like, [nonlimiting examples of these aesthetic components include clove oil, menthol, camphor, eucalyptus

oil, eugenol, menthyl lactate, witch hazel distillate, bisabolol, dipotassium glycyrrhizinate and the like]; and skin conditioning agents such as urea and glycerol, and also the propoxylated glycerols described in U.S. Pat. No. 4,976,953, or Orr et al., issued Dec. 11, 1990, which is incorporated by reference herein in its entirety.

SUMM [0097] The **compositions** of the present invention comprise a safe and effective amount of one or more active ingredients of pharmaceutically-acceptable salts thereof. The term "safe and effective amount" as used herein, means an amount of an active ingredient high enough to modify the condition to be treated or to deliver the desired skin benefit, but low enough to avoid serious side effects, at a reasonable benefit to risk ratio within the scope of sound medical judgement. What is a safe and effective amount of the active ingredient will vary with the specific active, the ability of the active to penetrate through the skin, the age, health condition, and skin condition of the user, and other like factors.

SUMM [0098] Typically, the active ingredients of the present invention comprise from about 0.001% to about 20%, preferably from a bout 0.01% to about 15%, and more preferably from about 0.025% to about 10% by weight of the **composition**.

SUMM [0099] The active ingredients useful herein can be categorized by their therapeutic benefit or their postulated mode of action. However, it is to be understood that the active ingredients useful herein can in some instances provide more than one therapeutic benefit or operate via more than one mode of action. Therefore, classifications herein are made for the sake of convenience and are not intended to limit the active ingredient to that particular application or applications listed. Also, pharmaceutically-acceptable salts of these active ingredients are useful herein. The following active ingredients are useful in the **compositions** of the present invention.

SUMM [0107] Sunscreen Actives: Also useful herein are sunscreening actives. A wide variety of sunscreening agents are described in U.S. Pat. No. 5,087,445, to Haffey et al., issued Feb. 11, 1992; U.S. Pat. No. 5,073,372, to Turner et al., issued Dec. 17, 1991; U.S. Pat. No. 5,073,371, to Turner et al. issued Dec. 17, 1991; and Segarin, et al., at Chapter VIII, pages 189 et seq., of Cosmetic Science and Technology, all of which are incorporated herein by reference in their entirety. Nonlimiting examples of sunscreens which are useful in the **compositions** of the present invention are those selected from the group consisting of 2-ethylhexyl p-methoxycinnamate, 2-ethylhexyl-N,N-dimethyl-p-aminobenzoate, p-aminobenzoic acid, 2-phenylbenzimidazole-5-sulfonic acid, octocrylene, oxybenzone, homomenthyl salicylate, octyl salicylate, 4,4'-methoxy-t-butyldibenzoylmethane, 4-isopropy dibenzoylmethane, 3-benzylidene camphor, 3-(4-methylbenzylidene) camphor, titanium dioxide, zinc oxide, silica, iron oxide, and mixtures thereof. Still other useful sunscreens are those disclosed in U.S. Pat. No. 4,937,370, to Sabatelli, issued Jun. 26, 1990; and U.S. Pat. No. 4,999,186, to Sabatelli et al., issued Mar. 12, 1991; these two references are incorporated by reference herein in their entirety. The sunscreening agents disclosed therein have, in a single molecule, two distinct chromophore moieties which exhibit different ultraviolet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range. These sunscreening agents provide higher efficacy, broader UV absorption, lower skin penetration and longer lasting efficacy relative to conventional sunscreens. Especially preferred examples of these sunscreens include those selected from the group consisting of 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2,4-dihydroxybenzophenone, 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid

ester with 4-hydroxydibenzoylmethane, 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)-benzophenone, 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 4-(2-hydroxyethoxy)-dibenzoylmethane, and mixtures thereof. Generally, the sunscreens can comprise from about 0.5% to about 20% of the **compositions** useful herein. Exact amounts will vary depending upon the sunscreen chosen and the desired Sun Protection Factor (SPF). SPF is a commonly used measure of photoprotection of a sunscreen against erythema. See Federal Register, Vol. 43, No. 166, pp. 38206-38269, Aug. 25, 1978, which is incorporated herein by reference in its entirety.

SUMM [0112] The **compositions** of the present invention can also comprise one or more humectants or moisturizers. A variety of these materials can be employed and each can be present at a level of from about 0.1% to about 20%, more preferably from about 0.5% to about 15%, and most preferably from about 1% to about 10%. Nonlimiting examples of humectants include materials selected from the group consisting of guanidine; glycolic acid and glycolate salts (e.g., ammonium and quaternary alkyl ammonium); lactic acid and lactate salts (e.g., ammonium and quaternary alkyl ammonium); aloe vera in any of its variety of forms (e.g., aloe vera gel); polyhydroxy alcohols such as sorbitol, glycerol, hexanetriol, propylene glycol, butylene glycol, hexylene glycol and the like; polyethylene glycols; sugars and starches; sugar and starch derivatives (e.g., alkoxylated glucose); hyaluronic acid; lactamide monoethanolamine; acetamide monoethanolamine; and mixtures thereof. Also, useful are propoxylated glycerols as described in U.S. Pat. No. 4,976,953, to Orr et al., issued Dec. 11, 1990, which is incorporated by reference herein in its entirety.

SUMM [0115] The **compositions** of the present invention can comprise from about 0.1% to about 20%, more preferably from about 0.25% to about 15%, and most preferably from about 0.5% to about 10%, based on the weight of the total **composition**, of insoluble particles which are useful for enhancing the cleansing effect, when the **compositions** of the present invention are in the form of a cleansing **composition**.

SUMM [0116] The term "insoluble", as used herein, means that the particles are essentially insoluble in the **compositions** of the present invention. In particular, the insoluble particles should have a solubility less than about 1 gram per 100 grams of **composition** at 25 degree C., preferably less than about 0.5 grams per 100 grams of **composition** at 25 degree C., and more preferably less than about 0.1 grams per 100 grams of **composition** at 25 degree C.

SUMM [0122] The **compositions** herein can comprise various emulsifiers. These emulsifiers are useful for emulsifying the various carrier components of the **compositions** herein. Suitable emulsifiers can include any of a wide variety of nonionic, cationic, anionic, and zwitterionic emulsifiers disclosed in the prior patents and other references. See McCutcheon's, Detergents and Emulsifiers, North American Edition (1986), published by Allured Publishing Corporation; U.S. Pat. No. 5,011,681 to Ciotti et al., issued Apr. 30, 1991; U.S. Pat. No. 4,421,769 to Dixon et al., issued Dec. 20, 1983; and U.S. Pat. No. 3,755,560 to Dickert et al., issued Aug. 28, 1973; these four references are incorporated herein by reference in their entirety.

SUMM [0124] The emulsifiers can be used individually or as a mixture of two or more and can comprise from about 0.1% to about 10%, more preferably from about 0.15% to about 7%, and most preferably from about 0.2% to about 5% of the **compositions** of the present invention.

SUMM [0126] The **compositions** of the present invention can comprise from about 0.25% to about 40%, preferably from about 0.5% to about 25%,

and more preferably from about 0.75% to about 15% of an oil selected from the group consisting of mineral oil, petrolatum, C7-C40 branched chain hydrocarbons, C1-C30 alcohol esters of C1-C30 carboxylic acids, C1-C30 alcohol esters of C2-C30 dicarboxylic acids, monoglycerides of C1-C30 carboxylic acids, diglycerides of C1-C30 carboxylic acids, triglycerides of C1-C30 carboxylic acids, ethylene glycol monoesters of C1-C30 carboxylic acids, ethylene glucol diesters of C1-C30 carboxylic acids, propylene glycol monoesters of C1-C30 carboxylic acids, propylene glucol diesters of C1-C30 carboxylic acids, C1-C30 carboxylic acid monesters and polyesters of sugars, polydialkylsiloxanes, polydiarylsiloxanes, polyalkarylsiloxanes, cyclomethicones having 3 to 9 silicon atoms, vegetable oils, hydrogenated vegetable oils, polypropylene glycols, polypropylene glycol C4-C20 alkyl ethers, di C8-C30 alkyl ethers, and mixtures thereof.

SUMM [0137] The complexes that are believed to be formed from the amphoteric, anionic, and cationic surfactants of the present invention are preferably preprepared by the following procedures. The amphoteric and anionic surfactants are first combined in aqueous solution, thereby forming what is believed to be a dispersion of the complex between these two materials. This dispersion is then combined directly with an aqueous solution of the cationic surfactant. Alternatively, this dispersion can be added directly to a **composition** already containing the desired cationic surfactant.

SUMM [0139] The present invention also relates to methods wherein an effective amount of the **composition** of the present invention is applied to the skin. These **compositions** are useful for conditioning and treating dry skin and for providing active ingredients to the skin. A wide range of quantities of the **compositions** of the present invention can be used. Quantities which are typically applied can range from about 0.1 mg/cm2 to about 25 mg/cm2.

SUMM [0140] In further embodiments, the **compositions** of the present invention are useful for personal cleansing, especially for cleansing of the face and neck areas. Typically, a suitable or effective amount of the cleansing **composition** is applied to the area to be cleansed. Alternatively, a suitable amount of the cleansing **composition** can be applied via intermediate application to a washcloth, sponge, pad, cotton ball or other application device. If desired, the area to be cleansed can be premoistened with water. It has been found that the **compositions** of the present invention can be combined with water during the cleansing process and rinsed-off from the skin. Alternatively, the **composition** can be used along and wiped-off from the skin using a pad, cotton ball, tissue, or other like device. The cleansing process is typically a two-step process involving application of the **composition** followed either by rinsing of the produce with water or wiping without the use of water. Generally, an effective amount of **composition** to be used will depend upon the needs and usage habits of the individual.

DETD [0142] A leave-on lotion **composition** containing benzoyl peroxide is prepared by combining the following ingredients using conventional mixing techniques.

Ingredients	Weight Percent
Phase A	
Water	QS 100
Glycerin	4.00
Disodium EDTA	0.10
Carbomer	0.60
Acrylates/C10-30	

Alkylacrylates Crosspolymer	0.05
Phase B	
Stearyl Alcohol	2.25
Cetyl Alcohol	2.25
Steareth-100	0.50
Distearyl Dimethyl Ammonium Chloride	0.20
Phase C	
Triethanolamine	0.50
Phase D	
Lipoic acid derivative	1.0-20.0
Phase E	
Cetyl Dimethyl Betaine	1.00
Sodium Lauryl Sulfate	0.50

DETD [0144] The resulting leave-on **composition** is useful for preventing and treating acne (including rosacea) while being mild to the skin. Alternatively, a **composition** is prepared in which the cetyl dimethyl betaine is replaced with stearyl dimethyl betaine.

DETD [0145] A personal cleanser **composition** containing salicylic acid is prepared by combining the following ingredients using conventional mixing techniques.

Ingredients	Weight Percent
Phase A	
Water	QS 100
Glycerin	3.00
Disodium EDTA	0.01
Phase B	
PPG-15 Stearyl Ether	4.00
Stearyl Alcohol	2.88
Distearyl Dimonium Chloride	1.50
Cetyl Alcohol	0.80
Steareth-21	0.50
Behenyl Alcohol	0.32
PPG-30	0.25
Steareth-2	0.25
Phase C	
Lipoic acid derivative	1.00-20.00
Fragrance	0.27
Phase D	
Cocamidopropyl Betaine	2.00
Sodium Lauryl Sulfate	1.00

DETD [0147] The resulting cleansing **composition** is useful for preventing and treating skin damage induced by sunlight (UV radiation) and for cleansing the skin. Alternatively, a **composition** is prepared in which the sodium lauryl sulfate is replaced with sodium lauroyl isetheonate.

DETD [0150] The resulting cleansing **composition** is useful for cleansing the skin, for preventing or ameliorating skin dryness and wrinkle formation in the skin, for preventing thinning of the skin, for increasing the thickness, hydration and pliability of the skin, and for inhibiting the aging process in skin. Alternatively, a **composition** is prepared in which the menthol is eliminated and the water level is correspondingly increased.

DETD [0151] Alternatively, a **composition** is prepared in which the sodium lauryl sulfate is replaced with sodium lauroyl isetheonate.

DETD [0152] A leave-on cream **composition** is prepared by combined the following ingredients using conventional mixing techniques.

Ingredients	Weight Percent
Phase A	

Water	QS 100
Glycerin	5.00
Disodium EDTA	0.10
Methylparaben	0.20
Phase B	
PPG-15 Stearyl Ether	4.00
Stearyl Alcohol	1.44
Distearyl Dimonium Chloride	0.50
Cetyl Alcohol	0.40
Steareth-21	0.50
Behenyl Alcohol	0.16
Steareth-2	0.15
Propylparaben	0.10
Phase C	
Fragrance	0.12
Lipoic acid derivative	1.0-20.0
Phase D	
Cetyl Dimethyl Betaine	1.00
Sodium Lauryl Sulfate	0.50

DETD [0154] The resulting leave-on cream is useful for conditioning the skin and provides a soft/smooth skin feel. for preventing or ameliorating skin dryness, for preventing thinning of the skin, for increasing the thickness, hydration and pliability of the skin, and for inhibiting the aging process in skin. Alternatively, a **composition** is prepared in which the sodium lauryl sulfate is replaced with sodium lauroyl isetheonate.

DETD [0155] A leave-on lotion **composition** containing a lipoic acid derivative is prepared by combining the following ingredients using conventional mixing techniques.

Ingredients	Weight Percent
Phase A	
Water	QS 100
Glycerin	3.00
Tetrasodium EDTA	0.02
Phase B	
PPG-15 Stearyl Ether	4.00
Stearyl Alcohol	0.75
Salicylic Acid	2.00
Cetyl Alcohol	0.75
Steareth-21	0.45
Steareth-2	0.05
Distearyl Dimethyl Ammonium Chloride	0.75
Polyquatemium-37 (and) Mineral Oil (and) PPG-1 Trideceth-6	0.75
Phase C	
Triethanolamine	0.15
Phase D	
Lipoic acid derivative	1.0-20.0
Fragrance	0.10
Phase E	
Cetyl Dimethyl Betaine	2.00
Sodium Lauryl Sulfate 1.00	

DETD [0158] The resulting leave-on **composition** is useful for preventing treating acne while being mild to the skin and providing a soft/smooth skin feel, and for preventing or ameliorating skin dryness and wrinkle formation in the skin, for preventing thinning of the skin, for increasing the thickness, hydration and pliability of the skin, and for inhibiting the aging process in skin. Alternatively, a **composition** is prepared in which the sodium lauryl sulfate is replaced with sodium lauroyl isetheonate.

DETD [0160] The following alternative formulations demonstrate the typical

use of the protective skin **composition** of the present invention in skin care and over the counter (OTC) pharmaceutical products. These formulations are listed only as examples of the types of **compositions** that could be used, and are not all encompassing of the possible uses of the technology in skin care and OTC pharmaceutical products. One skilled in the art of formulation will readily envision other possible uses for this technology, and the invention is not restricted the use of the formulations listed below. All ingredients of the formulations listed below are shown in percentage by weight (% w/w). The following is a general formula for ligand formulations of the **composition**.

Materials	General Use Range (Wt %)
Purified Water	19.00000-98.71330
Surfactants	0.50-5.00
Lipoic acid derivative	1.0-20.0
Humectant	0.50-5.00
Fragrance	0.001-1.00
Preservatives	0.20-3.00
Sequestering Agent	0.01-0.50
Menthol	0.005-1.00
Vitamin A Palmitate	0.0005-0.50
Vitamin B Acetate	0.05-30.00
Magnesium Ascorbyl Phosphate	0.0001-3.00
Beta Glucan	0.005-5.00
Superoxide Dismutase	0.0001-1.00
Grape Seed Extract	0.00001-1.00
Panthenol	0.005-5.00
Total	100.00000%

DETD [0162] The following **composition** is useful for preventing treating acne (including rosacea) while being mild to the skin and providing a soft/smooth skin feel, and for preventing or ameliorating skin dryness and wrinkle formation in the skin, for preventing thinning of the skin, for increasing the thickness, hydration and pliability of the skin, and for inhibiting the aging process in skin.

Materials	Specific Use Concentration (Wt %)
Purified Water	79.4719
Surfactants	2.0000
Witch Hazel Distillate	15.0000
Humectant	1.0000
Lipoic acid derivative	1.0-20.0
Fragrance	0.0350
Preservatives	1.9000
Sequestering Agent	0.1000
Menthol	0.0100
Plant Extracts	0.0700
Vitamin A Palmitate	0.0050
Vitamin B Acetate	0.1000
Magnesium Ascorbyl Phosphate	0.0040
Beta Glucan	0.1000
Superoxide Dismutase	0.0040
Grape Seed Extract	0.0001
Panthenol	0.2000
Total	100.0000%

DETD [0164] The following oil-in-water formulation was developed as a moisturizing lotion for the skin.

Materials	Specific Use Concentration (Wt %)
Purified Water	79.4719
O/W Emulsifiers	11.0000
Humectants	5.0000
Fragrance	0.0500
Preservatives	2.7000
Sequestering Agent	0.1000
Emollients	12.0000
Thickeners	0.3000
Vitamin A Palmitate	0.0500
Vitamin E Acetate	1.0000
Magnesium Ascorbyl Phosphate	0.2500
Beta Glucan	1.0000
Superoxide Dismutase	0.0400
Grape Seed Extract	0.0050
Panthenol	2.0000
Lipoic acid derivative	1.0-20.0
Total	100.0000%

DETD [0166] The following is a general formulation for a moisturizing soap bar.

Materials	General Use Range (Wt %)
Purified Water	0.00-15.00
Detergents and Cleansing Agents	32.0000-97.9573
Buffering Agents	1.00-3.00
Humectants and Skin Conditioning Agents	0.50-5.00
Fragrance	0.001-1.00
Preservatives	0.01-2.00
Thickeners and Coloring Agents	0.01-30.00
Vitamin A Palmitate	0.0005-0.50
Vitamin E Acetate	0.05-30.00
Magnesium Ascorbyl Phosphate 0.0001-3.00	
Beta Glucan	0.005-5.00
Superoxide Dismutase	0.0001-1.00
Grape Seed Extract	0.00001-1.00
Panthenol	0.005-5.00
Lipoic acid derivative	1.0-20.0
Total	100.00000%

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DETD [0167] Moisturizing soap bar for sensitive facial skin

Materials	Specific Use Concentration (Wt %)
Purified Water	9.3400
Detergents and Cleansing Agents	48.2000
Buffering Agents	2.4800
Humectants and Skin Conditioning Agents	13.0870
Fragrance	0.2400
Preservatives	0.0900
Thickeners and Colorants	25.6600
Vitamin A Palmitate	0.0050

Vitamin E Acetate	0.4900
Magnesium Ascorbyl Phosphate	0.0040
Beta Glucan	0.0100
Superoxide Dismutase	0.0040
Grape Seed Extract	0.1950
Panthenol	0.1950
Lipoic acid derivative	1.0-5.0
Total	100.0000%

DETD [0168] The following **compositions** are disclosed herein. A first compound of this invention is disclosed as: ##STR1##

DETD [0448] Moisturizing soap bar for sensitive facial skin

Materials	Specific Use Concentration (Wt %)
Purified Water	9.3400
Detergents and Cleansing Agents	48.2000
Buffering Agents	2.4800
Humectants and Skin Conditioning Agents	13.0870
Fragrance	0.2400
Preservatives	0.0900
Thickeners and Colorants	25.6600
Vitamin A Palmitate	0.0050
Vitamin E Acetate	0.4900
Magnesium Ascorbyl Phosphate	0.0040
Beta Glucan	0.0100
Superoxide Dismutase	0.0040
Grape Seed Extract	0.1950
Panthenol	0.1950
Lipoic acid derivative	1.0-5.0
Total	100.0000%

DETD [0449] The above moisturizing facial soap **composition** provides improved skin feel useful for conditioning desquamating, and cleansing the skin and for relieving dry skin.

DETD [0463] 1. U.S. Pat. No. 6,149,925 Mammone et al: Topical **compositions** for enhancing glutathione production

DETD [0464] 2. U.S. Pat. No. 6,180,133 Quan et al: Antioxidant **composition** for topicautransdermal prevention and treatment of wrinkles

DETD [0465] 6,180,133 McAtee et al: Antioxidant **composition** for topical/transdermal prevention and treatment of wrinkles

DETD [0467] 5. U.S. Pat. No. 6,153,204 Fanger et al: Cosmetic or pharmaceutical **preparations** with a reduced feeling of stickiness

DETD [0470] 8. U.S. Pat. No. 5,948,810 Wessel et al: Use of R-(+)-.alph.alpha.-lipoic acid, R-(-)-dihydrolipoic acid and metabolites in the form of the free acid or as salts or esters or amides for the **preparation** of drugs for the treatment of diabetes mellitus as well as of its sequelae

DETD [0471] 9. U.S. Pat. No. 5,728,735 Ulrich et al: Pharmaceutical **composition** containing R-alpha.-lipoic acid or S-alpha.-lipoic acid as active ingredient

DETD [0472] 10. U.S. Pat. No. 5,607,980 McAtee et al: Topical **compositions** having improved skin feel

DETD [0473] 11. U.S. Pat. No. 5,709,868 Perricone: Lipoic acid in topical **compositions**

DETD **Preparation** and Uses of 1,2-Dithiolan-4-yl and 3-yl Alkanoic Acids, .alpha.-Hydroxy Acids, Pyruvates and Related Amides and Hydroxamic Acids

DETD Mitchell A. Avery, **Ph**.D. and Harrihar Pershadsingh, M.D., **Ph**.D.

DETD [0494] Other than tetranorisolipoic acid 6 shown in Scheme 1,.sup.2-3

and isolipoic acid 2,.sup.4 the isolipoic acids 1, 3, 4 and 5 do not appear to have been prepared. Except for limited commerical dermatological applications, the biological effects of tetranorisolipoic acid 6.sup.5,6 have not been examined. Asparagusic acid 6 is, on the other hand, more well known for its phytochemical properties..sup.7,8. Since one would predict that the antioxidant behavior of these species should be comparable to or better than the well known naturally occurring lipoic acids,.sup.9 their **preparation**, antioxidant behavior, medical and cosmetic applications.sup.5,6 are of interest. Furthermore, the lack of a chiral center in these isolipoic acids (1,2-dithiolan-4-yl) is advantageous compared to the lipoic acids (1,2-dithiolan-3-yl) that possess different biological effects for each of the enantiomers..sup.1 ##STR6##

DETD [0519] The same chemistry applied to the aldehyde 74 should be possible, furnishing the requisite triol 75 for **preparation** of lipoic acid analogs as shown in Scheme 12. Removal of the pivalate ester with base should furnish alcohol 76, oxidation of which to acid should be possible with pyridinium dichromate in DMF. The acid could then be converted to the oxazolidinone as in Scheme 11, converted to the enone 78, and then processed identically to Scheme 11 to give the product dithiols 79-84. Deacylation and oxidation of the dithiols 79-84 should afford the dithiolanes 85-90.

DETD [0521] While the organozinc chemistry exemplified in Scheme 12 could be used to prepare these chiral 1,3-diols leading to the target molecules, there are a plethora of methods in the chemical literature for their **preparation**. Therefore, other methods could be as readily employed to arrive at structures such as 75, 76 or 77 and this method is not intended to indicate the only available methodology. One such alternative route is shown in Scheme 13. Deprotonation of the protected 1,3-diol 97 in the presence of (-)-sparteine leads to formation of a chiral organolithium whose configuration is retained in the ensuing alkylation to furnish S-alcohol products 98..sup.22,23 ##STR21##

CLM What is claimed is:

6. A method for treating, ameliorating, preventing or reversing diseases or conditions related to or caused by free radicals or reactive oxygen species and the resultant oxidative stress imposed by the generation of free radicals or reactive oxygen species, by administering to human or warm-blooded animal in need, a therapeutically or cosmetically effective amount of a pharmaceutical **composition** or cosmetic **preparation** wherein said **composition** or **preparation** is a compound of this invention, or a salt, solvate, tautomer or stereoisomer thereof.

7. The method of claim 6 wherein the disease or condition is related to an inflammatory, proliferative, metabolic or degenerative pathology, resulting from a genetic or hereditary predisposition or an environmental insult, induced by oxidative stress and the resultant generation of free radicals, oxidants and activated oxygen species, said method comprising administering to a human or warm-blooded animal in need, A) a therapeutically effective amount of a pharmaceutical **composition** or cosmetically effective amount of a compound of this invention, or a pharmaceutically or cosmetically acceptable salt, solvate, tautomer or stereoisomer thereof, in a pharmaceutically or cosmetically acceptable carrier.

14. The method of claim 6 comprising a cosmetic **preparation** for treating sun-damaged skin, dry skin, chapped skin, wrinkled skin, aging skin, sagging skin, rough skin, weathered skin, inflammed skin, reddened skin, psoriasis, keratitis, hidradenitis, ichthyosis, acne, rosacea, verrucae and other HPV infections, atopic dermatitis, allergic dermatitis, chemical (irritant) dermatitis, seborrheic dermatitis, solar dermatitis, acute and chronic eczema, seborrheic keratosis, senile keratosis, actinic keratosis, photo-induced keratosis, skin aging, thinning skin, dry skin, wrinkle formation, photo-induced skin aging,

keloids, lichen planus, comprising a compound of this, or a cosmetically acceptable salt thereof.

15. The method of claim 6 wherein the therapeutic **composition** is administered orally.

16. The method of claim 6 wherein the pharmaceutical **composition** or cosmetic **preparation** is administered topically to the suface of the skin (epidermis), conjunctiva, cornea, mucous membranes, as a solution, gel, lotion, foam, ointment or shampoo, as deemed appropriate to one skilled in the art.

17. The method of claim 6 wherein the pharmaceutical **composition** or cosmetic **preparation** of this invention is administered in combination with one or more compounds selected from the group of organic acids, consisting of: palmitic, oleic, linoleic, linolenic, arachidonic, petroselenic acid, erucic acid, lauric acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), glycolic acid, lactic acid, pyruvic acid, succinic acid, or 8-(S)-hydroxyeicosatetraenoic acid, azelaic acid, or salts, solvates, tautomers or stereoisomers thereof.

18. The method of claim 6 wherein the pharmaceutical **composition** or cosmetic **preparation** of this invention is administered as a nutriceutical, for nutritional enhancement.

19. The method of claim 14 wherein the pharmaceutical **composition** or cosmetic **preparation** of this invention is administered as a cosmeceutical, for cosmetic enhancement, to soften skin, improve skin feel, improve skin texture, increase skin hydration, increase skin elasticity and springiness, enhance the integrity of the epidermal barrier.

IT 50-21-5, Lactic acid, biological studies 50-81-7D, Ascorbic acid, derivs. 57-10-3, Palmitic acid, biological studies 60-33-3, Linoleic acid, biological studies 68-26-8D, Retinol, derivs. 79-14-1, Glycolic acid, biological studies 110-15-6, Succinic acid, biological studies 112-80-1, Oleic acid, biological studies 112-86-7, Erucic acid 117-39-5D, Quercetin, derivs. 121-79-9D, Propyl gallate, derivs. **123-31-9D**, Hydroquinone, derivs. 123-99-9, Azelaic acid, biological studies 127-17-3, Pyruvic acid, biological studies 128-37-0D, BHT, derivs. 143-07-7, Lauric acid, biological studies 446-72-0D, Genistein, derivs. 463-40-1, Linolenic acid 486-66-8D, Daidzein, derivs. 506-32-1, Arachidonic acid 520-36-5D, Apigenin, derivs. 593-39-5 1200-22-2D, R-.alpha.-Lipoic acid, derivs. 1406-16-2D, Vitamin D, derivs. 1406-18-4D, Vitamin E, derivs. 1948-33-0D, TBHQ, derivs. 5694-54-2D, Isolipoic acid, derivs. 6217-54-5, Docosahexaenoic acid 10417-94-4, Eicosapentaenoic acid 25013-16-5D, BHA, derivs. 57828-26-9, Lipoic acid 98462-03-4, 8-(S)-Hydroxyeicosatetraenoic acid 127254-35-7D, S-.alpha.-Lipoic acid, derivs.
(lipoate derivs. as antioxidants for skin products and other uses assocd. with oxidative stress)

ACCESSION NUMBER: 2002:92280 USPATFULL
TITLE: Novel antioxidants
INVENTOR(S): Avery, Mitchell Allen, Oxford, MS, UNITED STATES
Pershadsingh, Harrihar A., Bakersfield, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002048798	A1	20020425
APPLICATION INFO.:	US 2001-809518	A1	20010314 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-189514P	20000315 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Harrihar A. Pershadsingh, 404 Windsor Park Drive, Bakersfield, CA, 93311	
NUMBER OF CLAIMS:	19	
EXEMPLARY CLAIM:	1	
LINE COUNT:	4281	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L72 ANSWER 8 OF 10 USPATFULL

SUMM In another embodiment, the present invention involves a topical skin exfoliation **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid. It may further comprise hydroquinone. In one embodiment, the **composition** is 16-14 parts L+ lactic acid, 18-24 parts citric acid, 2 parts kojic acid and 50 to 65 parts ethyl alcohol. A preferred topical skin exfoliation **composition** useful in skin peels involves 10-16 parts L+ lactic acid, 12-18 parts citric acid, 14 parts salicylic acid, 2 parts kojic acid and 50 to 65 parts ethyl alcohol.

SUMM a) obtaining a **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid;

SUMM b) applying a coating of said **composition** to the facial skin in an amount effective to cause skin peeling.

SUMM a) prior to applying said **composition**, thoroughly cleansing facial skin to be exfoliated using an appropriate degreaser;

SUMM b) applying a second coat of said **composition** to the facial skin 2 to 4 minutes after the first coat;

SUMM c) applying third and further coats of said **composition** to the facial skin at 2 to 4 minute intervals until appearance of crystals or "frosting";

SUMM None before have prepared a **composition** according to the present invention for the use of a superior skin exfoliation or peeling **composition**. Of course, neither has such **composition** been used in a method for such a procedure.

DETD Glycolic acid has the smallest molecule of the alpha hydroxy acids allowing for enhanced penetration into the dermal layers when conditions warrant. It is commercially available as a white crystalline compound that is 99% pure and also as a 70% aqueous solution. Preferred embodiments include addition of kojic acid and derivatives thereof along with additional components such as hydroquinone in the 1 to 2% range. Skin response to glycolic acid depends not only on its concentration and **pH** but also on other factors such as the amount of free acid delivered to the skin, the duration of contact, **preparation** of the skin before peeling, and the condition of the skin before treatment.

DETD The effect of the skin peeling treatment with and without hydroquinone was tested by comparative application of the method. In this example the subjects were directed to wash both arms with cleanser, consisting of acetone. The arms were then cleaned with a balancing toner. Then, four successive coats of the skin peeling **composition**, consisting of Example 3 were applied. Subjects were then directed to wipe off the dried film with more toner and to apply sunscreen to protect the treated skin. This was followed by a twice-daily regiment of wash, toner, and sunscreen.

DETD All of the **compositions** and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the **compositions** and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the **compositions** and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

CLM What is claimed is:

1. A therapeutic skin peel **composition** comprising a melanin inhibitor in combination with a hydroxy acid.

2. The **composition** of claim 1, wherein said melanin inhibitor comprises kojic acid or a derivative thereof.

3. The **composition** of claim 1, wherein said hydroxy acid is selected from the group consisting of an .alpha.-hydroxy acid, a .beta.-hydroxy acid or a keto acid.

4. The **composition** of claim 1, wherein said combination is in an ethyl alcohol/water carrier.

5. The **composition** of claim 3, wherein said .alpha.-hydroxy acid is selected from the group consisting of L-lactic acid, glycolic acid, tartaric acid and malic acid.

6. The **composition** of claim 3, wherein said .beta.-hydroxy acid is citric acid or L-ascorbic acid.

7. The **composition** of claim 3, wherein said keto acid is selected from the group consisting of L-ascorbic acid, salicylic acid and pyravic acid.

8. The **composition** of claim 5, wherein said .alpha.-hydroxy acid is malic acid.

9. The **composition** of claim 8, further comprising citric acid.

10. The **composition** of claim 9, further comprising a compound selected from the group consisting of hydroquinone, hydroquinone monobenzyl ether, and hydroquinone monoethyl ether.

11. The **composition** of claim 5, wherein said .alpha.-hydroxy acid is L-lactic acid.

12. The **composition** of claim 11, further comprising a .beta.-hydroxy acid.

13. The **composition** of claim 12, wherein said .beta.-hydroxy acid is citric acid.

14. The **composition** of claim 13, comprising 16 to 24 parts L(+) lactic acid, 18-24 parts citric acid and 2 parts kojic acid.

15. The **composition** of claim 12, further comprising a keto acid.

16. The **composition** of claim 15, wherein said keto acid is

salicylic acid.

17. The **composition** of claim 16, comprising 10 to 16 parts L(+) lactic acid, 12 to 18 parts citric acid, 14 parts salicylic acid and 2 parts kojic acid.

18. A therapeutic skin peeling **composition** comprising at least one skin exfoliating agent and at least one melanin-inhibiting agent.

19. The **composition** of claim 18, further comprising at least one melanin bleaching agent.

20. The **composition** of claim 18, wherein said skin exfoliating agent is selected from the group consisting of salicylic acid, glycolic acid, retinoic acid, resorcinol, and pyruvic acid.

21. The **composition** of claim 20, wherein said skin exfoliating agent is glycolic acid.

22. The **composition** of claim 20, wherein said melanin-inhibiting agent is selected from the group consisting of gamma-L-glutamyl-L cysteine, gamma-L-cysteine, oxidized glutathione, polyphenol, linoleic acid, ellagic acid, glycyrrhizic acid, alkylsalicylic acid, kojic acid glycosides, kojic acid succinimide ester, thiazoles, propionic acid, sulphur, kojic acid, ascorbates and urea, L-ascorbate, kudzu roots, lavanols, caffeic acid, dicaffeoylquinic acid, tricaffeoylquinic acid, vitamin K, **ascorbic acid phosphate magnesium** salt, kojic acid dimer, hydantoin, tranexamic acid, chromone derivative, indomethicin methacin, erthorbic acid glucoside, phenol (in low concentration), niacinimide, cinnamic acid, conchiolin hydrolyzate, licorice root extract, hydroquinone, logwood extract, gromwell seed extract, arbutin, chitosans, superoxide dismutase, melanostatin, S-lactoyl glutathione, cystamine, buthionine sulfoximine, Feldamycin, glycyrrhetinic acid, phenylthioruea, glucosamine, ferulic acid, fuzi acid derived from conitum root, 5,6-dihydroxyindole, arginine, benzophenone, lysine and/or its derivatives, polylysine, linoleic acid, magnesium ascorbate, S-lactoyl glutathione, and hydroquinone glycoside.

23. The **composition** of claim 22, wherein said melanin-inhibiting agent is kojic acid.

24. The **composition** of claim 23, wherein said skin exfoliating agent is glycolic acid.

25. The **composition** of claim 23, wherein said skin exfoliating agent is salicylic acid.

26. The **composition** of claim 19, wherein said melanin bleaching agent is selected from the group consisting of citric acid, lactic acid, ascorbic acid, and azelaic acid.

27. The **composition** of claim 19, wherein said melanin bleaching agent may also act as a melanin-inhibiting agent.

28. The **composition** of claim 27, wherein said melanin bleaching agent is selected from the group consisting of arbutin, kojic acid, hydroquinone, superoxide dismutase, and gromwell seed extract.

29. The **composition** of claim 26, wherein said skin exfoliating agent is salicylic acid.

30. The **composition** of claim 29, wherein said melanin-inhibiting agent is kojic acid.

31. The **composition** of claim 30, futher comprising citric acid, lactic acid and ascorbic acid.

32. The **composition** of claim 31, comprising 10 to 16 parts L-lactic acid, 12 to 18 parts citric acid, 14 parts salicylic acid, 2 parts kojic acid and 2 parts ascorbic acid.

33. The **composition** of claim 18, further comprising at least one skin-penetrating agent.

34. The **composition** of claim 33, wherein said skin-penetrating is selected from the group consisting of urea, aloe vera, casein, lactic acid and an .alpha.-hydroxy mixture.

35. A method for facial exfoliation comprising (a) obtaining a therapeutic skin peeling **composition** comprising kojic acid or a derivative thereof and at least one acid selected from the group consisting of an .alpha.-hydroxy acid, a .beta.-hydroxy acid, and a keto acid in an ethyl alcohol/water carrier; (b) applying a first coating of said **composition** to the facial skin in a manner effective to cause skin peeling; and (c) cleansing facial skin with water.

36. The method of claim 35, further comprising thoroughly cleansing facial skin prior to first application of said **composition** with a degreaser.

38. The method of claim 35, further comprising applying a second coating of said **composition** 2 to 4 minutes after first application of said **composition**.

39. The method of claim 36, further comprising applying a second coating of said **composition** 2 to 4 minutes after first application of said **composition**.

40. The method of claim 38, further comprising applying additional coatings of said **composition** 2 to 4 minutes after the previous application as needed until the appearance of crystals or "frosting".

41. The method of claim 39, further comprising applying additional coatings of said **composition** 2 to 4 minutes after the previous application as needed until the appearance of crystals or "frosting".

IT 50-81-7, Ascorbic acid, biological studies 51-85-4, Cystamine 52-90-4, L-Cysteine, biological studies 53-86-1, Indomethacin 56-87-1, L-Lysine, biological studies 57-13-6, Urea, biological studies 60-33-3, Linoleic acid, biological studies 64-17-5, Ethanol, biological studies 69-72-7, Salicylic acid, biological studies 74-79-3, L-Arginine, biological studies 77-92-9, Citric acid, biological studies 79-09-4, Propionic acid, biological studies 98-92-0, Niacinamide 103-85-5, Phenylthiourea 108-46-3, Resorcinol, biological studies 108-95-2, Phenol, biological studies 119-61-9, Benzophenone, biological studies **123-31-9**, Hydroquinone, biological studies 123-99-9, Azelaic acid, biological studies 302-79-4, Retinoic acid 331-39-5, Caffeic acid 461-72-3, Hydantoin 471-53-4, Glycyrrhetinic acid 476-66-4, Ellagic acid 491-38-3D, Chromone, derivs. 497-76-7, Arbutin 501-30-4D, Kojic acid, succinimide ester 621-82-9, Cinnamic acid, biological studies 1135-24-6, Ferulic acid 1182-34-9, Dicaffeoylquinic acid 1197-18-8, Tranexamic acid 1405-86-3, Glycyrrhizic acid 3131-52-0, 5,6-Dihydroxyindole 3416-24-8, Glucosamine 5072-26-4, Buthionine sulfoximine 5466-77-3, Octyl p-methoxycinnamate 7704-34-9, Sulfur, biological studies 9012-76-4, Chitosan 9054-89-1, Superoxide dismutase 9083-38-9, Melanostatin 12001-79-5, Vitamin K 13463-67-7, Titania, biological studies

15431-40-0, Magnesium ascorbate 25104-18-1, Polylysine 25138-66-3, S-Lactoylglutathione 27025-41-8, Oxidized glutathione 38000-06-5, Polylysine 56328-22-4 61230-27-1, Feldamycin **108910-78-7** 124134-09-4 154160-11-9
(.alpha.-hydroxy acid-kojic acid skin peel)

ACCESSION NUMBER: 2001:173623 USPATFULL
TITLE: Hydroxy-kojic acid skin peel
INVENTOR(S): Ancira, Margaret, 6850 N. 83rd St., Scottsdale, AZ, United States 85250

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6300369	B1	20011009
APPLICATION INFO.:	US 1999-299788		19990222 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-795231, filed on 10 Feb 1997, now patented, Pat. No. US 5874463 Continuation-in-part of Ser. No. US 1994-328006, filed on 24 Oct 1994
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FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Lambkin, Deborah C.
LEGAL REPRESENTATIVE: Fulbright & Jaworski
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NUMBER OF DRAWINGS: 9 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 653
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L72 ANSWER 9 OF 10 USPATFULL

SUMM In another embodiment, the present invention involves a topical skin exfoliation **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid. It may further comprise hydroquinone. In one embodiment, the **composition** is 16-14 parts L+ lactic acid, 18-24 parts citric acid, 2 parts kojic acid and 50 to 65 parts ethyl alcohol. A preferred topical skin exfoliation **composition** useful in skin peels involves 10-16 parts L+ lactic acid, 12-18 parts citric acid, 14 parts salicylic acid, 2 parts kojic acid and 50 to 65 parts ethyl alcohol.

SUMM a) obtaining a **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid;

SUMM b) applying a coating of said **composition** to the facial skin in an amount effective to cause skin peeling.

SUMM a) prior to applying said **composition**, thoroughly cleansing facial skin to be exfoliated using an appropriate degreaser;

SUMM b) applying a second coat of said **composition** to the facial skin 2 to 4 minutes after the first coat;

SUMM c) applying third and further coats of said **composition** to the facial skin at 2 to 4 minute intervals until appearance of crystals or "frosting";

SUMM None before have prepared a **composition** according to the present invention for the use of a superior skin exfoliation or peeling **composition**. Of course, neither has such **composition** been used in a method for such a procedure.

DETD Glycolic acid has the smallest molecule of the alpha hydroxy acids allowing for enhanced penetration into the dermal layers when conditions warrant. It is commercially available as a white crystalline compound

that is 99% pure and also as a 70% aqueous solution. Preferred embodiments include addition of kojic acid and derivatives thereof along with additional components such as hydroquinone in the 1 to 2% range. Skin response to glycolic acid depends not only on its concentration and **pH** but also on other factors such as the amount of free acid delivered to the skin, the duration of contact, **preparation** of the skin before peeling, and the condition of the skin before treatment.

DETD The effect of the skin peeling treatment with and without hydroquinone was tested by comparative application of the method. In this example the subjects were directed to wash both arms with cleanser, consisting of acetone. The arms were then cleaned with a balancing toner. Then, four successive coats of the skin peeling **composition**, consisting of Example 3 were applied. Subjects were then directed to wipe off the dried film with more toner and to apply sunscreen to protect the treated skin. This was followed by a twice-daily regiment of wash, toner, and sunscreen.

DETD All of the **compositions** and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the **compositions** and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the **compositions** and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

CLM What is claimed is:

1. A method for skin peeling comprising application of a skin peel **composition** comprising at least about 28 parts alpha hydroxy acid, about 14 parts salicylic acid and about 2 parts kojic acid followed by skin exfoliation to produce clinically visible skin plumpness with reduced hyperpigmentation.

2. A method for skin peeling with reduction of acne comprising application of a skin peel **composition** comprising kojic acid, about 14 parts salicylic acid and at least 28 parts alpha hydroxy acid selected from the group consisting of lactic acid, glycolic acid and citric acid, followed by facial skin exfoliation to produce clinically visible skin plumpness with reduced acne.

3. A method for the treatment of skin photodamage comprising application of a skin peel **composition** comprising at least 28 parts of one or more of glycolic, lactic and citric acid, about 14 parts salicylic acid and about 2 parts kojic acid, followed by skin exfoliation to produce clinically visible skin plumpness with reduced photodamage.

4. A method for facial exfoliation, comprising the following steps: a) obtaining a **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid in amounts effective to induce skin peeling; b) applying a coating of said **composition** to the facial skin in a manner effective to cause skin peeling; and c) removing exfoliating skin.

5. The method of claim 4, further comprising: a) prior to applying said **composition**, thoroughly cleansing facial skin to be exfoliated using an appropriate degreaser; b) applying a second coat of said **composition** to the facial skin 2 to 4 minutes after the first coat; c) applying third and further coats of said **composition** to the facial skin at 2 to 4 minute intervals until appearance of crystals or "frosting"; d) cleaning the facial skin with a water

dampened sponge or equivalent; e) applying hydrator mixture comprising octylmethoxy cinnaminate, benzophenone 3 and titanium dioxide in aloe vera solution the first night after peel; and f) performing additional treatments at biweekly or monthly intervals until desired results are obtained.

7. A topical skin exfoliation **composition** comprising lactic acid, kojic acid, citric acid and salicylic acid.

8. A topical skin exfoliation **composition** comprising lactic acid, kojic acid, citric acid, hydroquinone and salicylic acid.

9. A topical skin exfoliation **composition** comprising kojic acid, at least one alpha hydroxy acid and salicylic acid.

10. A topical skin exfoliation **composition** comprising 16 to 24 parts L(+) lactic acid, 18 to 24 parts citric acid, 2 parts kojic acid, and 50 to 65 parts ethyl alcohol.

11. A topical skin exfoliation **composition** comprising salicylic acid and kojic acid.

12. The **composition** of claim 7, defined further as comprising hydroquinone.

13. A topical skin exfoliation **composition** comprising 10 to 16 parts L(+) lactic acid, 12 to 18 parts citric acid, 14 parts salicylic acid, 2 parts kojic acid, and 50 to 65 parts ethyl alcohol.

14. A topical skin exfoliation **composition** comprising kojic acid.

15. A topical skin exfoliation **composition** comprising kojic acid and lactic acid.

16. A topical exfoliation **composition** comprising at least one skin exfoliating agent selected from the group consisting of salicylic acid; glycolic acid, retinoic acid; resorcinol, and pyruvic acid and at least one melanin-inhibiting agent selected from the group consisting of gamma-L-glutamyl-L cystine, gamma-L-cysteine, oxidized glutathione, polyphenol, linoleic acid, ellagic acid, glycyrrhizic acid, alkylsalicylic acid, kojic acid glycosides, kojic acid succinimide ester, thiazoles, propionic acid, sulphur, kojic acid, ascorbates and urea, L-ascorbate, kudzu roots, lavanols, caffeic acid, dicaffeoylquinic acid, tricaffeoylquinic acid, vitamin K, **ascorbic acid phosphate magnesium** salt, kojic acid dimer, hydantoin, tranexamic acid, chromone derivative, indomethicin methacin, erthorbic acid glucoside, phenol (in low concentration), niacinimide, cinnamic acid, conchiolin hydrolyzate, licorice root extract, hydroquinone, logwood extract, gromwell seed extract, arbutin, chitosans, superoxide dismutase, melanostatin, S-lactoyl glutathione, cystamine, buthionine sulfoximine, Feldamycin, glycyrrhetinic acid, phenylthiourea, glucosamine, ferulic acid, fuzi acid derived from aconitum root, 5. 6-dihydroxyindole, arginine, benzophenone, lysine and/or its derivatives, polylysine, linoleic acid, magnesium ascorbate, S-lactoyl glutathione, and hydroquinone glycoside.

17. The **composition** of claim 16 further defined as comprising at least one skin-penetrating agent selected from the group consisting of urea, aloe vera, casein, lactic acid, and an alpha hydroxy acid mixture.

18. The **composition** of claim 16 further defined as comprising at least one melanin bleaching agent selected from the group consisting

of citric acid, lactic acid, ascorbic acid, arbutin, kojic acid, hydroquinone, superoxide dismutase, gromwell seed extract, and azelaic acid wherein some of the melanin bleaching agents also act as inhibitors for melanin formation.

IT 50-81-7, Ascorbic acid, biological studies 51-85-4, Cystamine 52-90-4, L-Cysteine, biological studies 53-86-1, Indomethacin 56-87-1, L-Lysine, biological studies 57-13-6, Urea, biological studies 60-33-3, Linoleic acid, biological studies 64-17-5, Ethanol, biological studies 69-72-7, Salicylic acid, biological studies 74-79-3, L-Arginine, biological studies 77-92-9, Citric acid, biological studies 79-09-4, Propionic acid, biological studies 98-92-0, Niacinamide 103-85-5, Phenylthiourea 108-46-3, Resorcinol, biological studies 108-95-2, Phenol, biological studies 119-61-9, Benzophenone, biological studies **123-31-9**, Hydroquinone, biological studies 123-99-9, Azelaic acid, biological studies 302-79-4, Retinoic acid 331-39-5, Caffeic acid 461-72-3, Hydantoin 471-53-4, Glycyrrhetinic acid 476-66-4, Ellagic acid 491-38-3D, Chromone, derivs. 497-76-7, Arbutin 501-30-4D, Kojic acid, succinimide ester 621-82-9, Cinnamic acid, biological studies 1135-24-6, Ferulic acid 1182-34-9, Dicaffeoylquinic acid 1197-18-8, Tranexamic acid 1405-86-3, Glycyrrhizic acid 3131-52-0, 5,6-Dihydroxyindole 3416-24-8, Glucosamine 5072-26-4, Buthionine sulfoximine 5466-77-3, Octyl p-methoxycinnamate 7704-34-9, Sulfur, biological studies 9012-76-4, Chitosan 9054-89-1, Superoxide dismutase 9083-38-9, Melanostatin 12001-79-5, Vitamin K 13463-67-7, Titania, biological studies 15431-40-0, Magnesium ascorbate 25104-18-1, Polylysine 25138-66-3, S-Lactoylglutathione 27025-41-8, Oxidized glutathione 38000-06-5, Polylysine 56328-22-4 61230-27-1, Feldamycin **108910-78-7** 124134-09-4 154160-11-9
(.alpha.-hydroxy acid-kojic acid skin peel)

ACCESSION NUMBER: 1999:24681 USPATFULL
TITLE: Hydroxy-kojic acid skin peel
INVENTOR(S): Ancira, Margaret, 6850 N. 83rd St., Scottsdale, AZ, United States 85250

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L72 ANSWER 10 OF 10 USPATFULL
TI Chemical **compositions** for inhibiting nitrosation reaction in toiletries and cosmetics
SUMM The present invention relates to the use of certain compounds to inhibit nitrosation reactions (especially the formation of N-nitrosamines), to **compositions** comprising such compounds and to various methods of inhibiting nitrosation reactions.

SUMM As noted in the Kirk-Othmer reference, nitrosamines have been shown to be carcinogenic in many animal species. Accordingly, it is desirable to reduce the levels of nitrosamines in **compositions** with which

humans and animals may come into contact, especially foodstuffs and consumer products such as toiletries, pharmaceuticals and cosmetics, but also in household and industrial products.

SUMM WO-A-9200122 (University of Missouri) describes polymers useful for scavenging nitrosating agents, which polymers may be used in **compositions** to prevent nitrosating agents from reacting with any amines present to form nitrosamines.

SUMM Casado et al ("Nitrite Ion as a Nitrosating Reagent. Nitrosation of Morpholine and Diethylamine in the Presence of Formaldehyde" J. Chem. Soc. Perkin Trans II (1984) pp 1963-1966) describe the kinetics of the nitrosation of morpholine and of diethylamine in the presence of formaldehyde at **pH** values from 6.5 to 8.2 and from 6.9 to 8.7 respectively. The authors propose a mechanism whereby the amines react with formaldehyde to form an iminium ion which then reacts with a nitrite ion to form a corresponding nitrosamine.

SUMM Preferably, the iminium ion scavenger is used in a system having a **pH** of from about 3 to about 12, suitably from about 6 to about 8.

SUMM Suitably, the iminium ion scavenger may be used in cosmetics products such as, for example, skin creams, lotions and foundations; in toiletries such as, for example, cleansing lotions, soaps and shampoos; in dental **preparations** such as mouthwashes and dentifrices; and in pharmaceutical **preparations** such as, for example, ointments, creams, lotions, syrups and suspensions. The scavenger may also be used in household products such as waxes, polishes, liquid detergents and surface cleaners and in industrial products such as metalworking fluids, adhesives, latexes, antifoams and paints. The present invention is well suited to use in products such as these which comprise a nitrosatable amine compound and a source of nitrite ions and/or formaldehyde, such as certain antimicrobial agents (e.g. the gem-bromonitro antimicrobials such as bronopol).

SUMM Preferably, the iminium ion scavenger is used in combination with a nitrite ion scavenger. The term "nitrite ion scavenger" as used herein denotes an agent which reacts with the nitrite ion more readily than does a nitrosatable amine such as morpholine. Suitably, the nitrite ion scavenger is chosen such that at a concentration of 1M, preferably 500 mM, preferably 100 mM, suitably 10 mM, it reduces the rate of formation of nitrosamines by at least about 25%, preferably at least about 50%, preferably at least about 75%, preferably at least about 90%, especially at least about 95% in a model system comprising 44 mM morpholine and 0.8 mM nitrite ions at **pH** 5 and 25.degree. C. Typically, nitrite ion scavengers are antioxidants such as ascorbate, isoascorbate, ascorbyl peptides, ascorbyl phosphates, (such as **magnesium ascorbyl phosphate** from Nikko Chemicals, Japan), butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), .alpha.-tocopherol, hydroquinone or catechol. As noted above, however, they may also be amines such as urea and hydrazide or amides such as methylsulphonamide or other compounds such as phenols, anilines and alkenes. The azide ion is also a nitrite ion scavenger, as it reacts with nitrite to form unstable nitrosyl azide which then decomposes to form nitrogen and nitrous oxide.

SUMM Use of an iminium ion scavenger in combination with a nitrite ion scavenger provides excellent inhibition of nitrosamine formation over a broad **pH** range (including the **pH** range from 3 to 12, especially the **pH** range from 4 to 8 typically found in cosmetics products) and over a broad temperature range (including the range of from around ambient temperature to about 45.degree. C. to which cosmetics products are typically subjected).

SUMM The present invention further provides a **composition** comprising a nitrosatable compound (especially a nitrosatable amine or amide), an effective amount of an iminium ion scavenger, an effective amount of a nitrite ion scavenger and a source or sources of nitrite ions and/or formaldehyde.

SUMM Preferably, the iminium ion scavenger is present at a concentration of from about 0.1 mM to about 1M, preferably from about 0.5 mM to about 50 mM, suitably from about 1 mM to about 25 mM and reduces the rate of nitrosation reactions by at least about 25%, preferably at least about 50%, preferably at least about 90%, especially at least about 95% at **pH** 7 and 25.degree. C. compared to a corresponding **composition** from which the scavenger is excluded.

SUMM Preferably, the nitrite ion scavenger is present at a concentration of from about 0.1 mM to about 1M, preferably from about 0.5 mM to about 50 mM, suitably from about 1 mM to about 25 mM and reduces the rate of nitrosation reactions by at least about 25%, preferably at least about 50%, preferably at least about 90%, especially at least about 95% at **pH** 5 and 25.degree. C. compared to a corresponding **composition** from which the scavenger is excluded.

SUMM Suitably, at a combined concentration of nitrite and iminium ion scavengers of from about 0.5 mM to about 1000 mM, preferably 1 mM to 50 mM, the inhibition of nitrosation reactions is at least about 50%, preferably at least about 75%, preferably at least about 80%, preferably at about 85% and preferably at least about 90% at 25.degree. C. between **pH** 5 and **pH** 8 compared to a corresponding **composition** from which the scavengers are excluded.

SUMM Suitably, the **composition** is a cosmetic, toiletry or pharmaceutical **composition** as described above.

SUMM Preferably, in such a **composition**, the iminium ion scavenger is sodium or potassium citrate, sodium or potassium fluoride, sodium or potassium adipate, or sodium or potassium dimethylglutarate.

SUMM Suitably, the **composition** comprises a gem-bromonitro antimicrobial agent such as 2-bromo-2-nitropropane-1,3-diol (BNPD; also known as "bronopol"), or another antimicrobial agent which gives rise to formaldehyde and/or nitrite, for example on decomposition.

SUMM Suitably, the **composition** is substantially free of phosphonic acid and/or phosphonates.

SUMM Preferably the **composition** has a **pH** of from 3 to 12, for example about 5 to 7.

SUMM Suitably, the gem-bromonitro antimicrobial agent is present at a concentration of from about 0.0001% by weight to about 1% by weight, typically about 0.02% by weight of the **composition**.

SUMM Preferably, the nitrite ion scavengers are used in a system having a **pH** of from about 1 to about 12, suitably from about 3 to about 10, for example from about 4 to 8, suitably about 5.

SUMM There is also provided a **composition** comprising a nitrosatable compound, an effective amount of a compound of Formula I above and a source or sources of formaldehyde and/or nitrite ions.

SUMM Suitably, the **composition** further comprises an iminium ion scavenger as defined above.

SUMM Suitably, the **composition** is a cosmetics, toiletries or pharmaceutical formulation such as those described above.

SUMM Suitably, the **composition** comprises a gem-bromonitro antimicrobial agent such as bronopol, or another such antimicrobial agent which releases nitrite and/or formaldehyde on decomposition.

SUMM Suitably, the **composition** is substantially free of phosphonic acid and/or phosphonates.

SUMM The invention further provides a concentrated **composition** consisting essentially of an antimicrobial agent giving rise to formaldehyde and/or nitrite ions on decomposition, an effective amount of an iminium ion scavenger and, optionally, an effective amount of a nitrite ion scavenger and, optionally, a carrier material such as water.

SUMM The term "**composition** consisting essentially of" as used herein denotes a **composition** which contains the components identified substantially free of significant quantities of other materials, for example a **composition** wherein the components listed make up about 75%, suitably about 90%, preferably about 99%, preferably substantially 100% of the **composition** by weight, volume and/or mole ratio.

SUMM The concentrated **compositions** according to the invention optionally further comprise suitable carriers and/or excipients. Advantageously the **compositions** may incorporate at least one buffering agent to minimise the fall of **pH** which may otherwise occur after dilution of the concentrated **composition**. The concentrated **compositions** may be provided in the form of packs containing one or more discrete units of an appropriate weight or volume for batch or unit dosing.

SUMM Concentrated **compositions** according to the invention may comprise substantially anhydrous mixtures of each of the components mentioned hereinbefore, optionally combined with suitable non-aqueous carriers or excipients. Such **compositions** may be in the form of, for example, powders, compressed tablets, capsules, or anhydrous solutions, pastes or suspensions. The **compositions** may be stored under anhydrous conditions for example in dessicators, hermetically sealed containers such as sachets, or in evacuated vials, ampoules or pump packs.

SUMM Concentrated solvated **compositions**, optionally combined with suitable carriers or excipients, may be packaged and maintained prior to use. They may be in the form of, for example, solutions, suspensions, emulsions, pastes or gels. Suitable solvents include water, ethyl and/or propyl alcohol, diethylene and/or dipropylene glycol and/or polyethylene glycol.

SUMM Where the **composition** comprises water it may be preferable to add a proportion of a polar organic co-solvent such as propylene or polyethylene glycol to prevent the **composition** freezing when, for example, the **composition** is stored at low temperatures.

SUMM Suitably, the **composition** comprises both an effective amount of iminium ion scavenger and an effective amount of a nitrite ion scavenger.

SUMM Suitably in such **compositions**, the antimicrobial agent is present in a molar ratio of from about 1:0.05 to 1:100, suitably from about 1:0.1 to 1:50, preferably from about 1:1 to 1:20, preferably from about 1:5 to 1:15, for example about 1:10, relative to the iminium ion scavenger or combination of iminium ion scavengers.

SUMM The invention also provides a **composition** consisting essentially of an antimicrobial agent giving rise to formaldehyde and/or nitrite ions on decomposition, an effective amount of hexamethylene-tetramine or a compound of formula I and, optionally, an iminium ion scavenger and, optionally, a carrier material, such as water.

SUMM The invention further provides a **composition** consisting essentially of an iminium ion scavenger or combination of iminium ion scavengers, a nitrite ion scavenger or a combination of nitrite ion scavengers and, optionally, a preservative and, optionally, a carrier material, such as water.

SUMM Thus, the invention further provides a **composition** consisting essentially of a nitrogenous raw material comprising a nitrosatable compound, an effective amount of an iminium ion scavenger and, optionally, an effective amount of a nitrite ion scavenger and, optionally, a carrier material such as water and, optionally, a preservative such as formaldehyde or bronopol. Preferably, the **composition** comprises effective amounts of both iminium and nitrite ion scavengers.

SUMM The invention also provides a **composition** consisting essentially of a nitrogenous raw material, an effective amount of hexamethylene tetramine or a compound of formula I above, and, optionally, an effective amount of an iminium ion scavenger and, optionally, a carrier material such as water and, optionally, a preservative such as formaldehyde or bronopol.

SUMM Suitably in such **compositions**, the nitrosatable amine is present in a molar ratio of from about 1:0.01 to 1:100, suitably from about 1:0.05 to 1:50, preferably from about 1:0.1 to 1:10, preferably about 1:1, relative to the iminium ion scavenger or combination of iminium ion scavengers.

SUMM The invention further provides a pharmaceutical **composition** comprising a nitrite ion scavenger and/or an iminium ion scavenger for use in the inhibition of nitrosamine formation in an animal. Suitably, the animal is a mammal such as man.

SUMM The invention further provides a pharmaceutical **composition** comprising a nitrosatable medicament such as a tetracycline, an iminium ion scavenger and, optionally a nitrite ion scavenger, together with a pharmaceutically acceptable diluent or carrier.

SUMM The therapeutic **compositions** of the present invention may take the form of any of the known pharmaceutical **compositions** for oral, rectal, parenteral or topical administration. The **compositions** may be formulated in a manner known to those skilled in the art so as to give a controlled release of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such **compositions** are well known in the art of pharmacy. The **compositions** of the invention suitably contain 0.1-90% by weight of active compound. The **compositions** of the invention are generally prepared in unit dosage form.

SUMM **Compositions** for oral administration are the preferred **compositions** of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oily suspensions. The excipients used in the **preparation** of these **compositions** are the excipients known in the pharmacists' art.

SUMM Tablets may be prepared by mixing the active compound with an inert diluent, such as lactose or calcium phosphate, in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. Such tablets may if desired be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly capsules, for example hard or soft gelatin capsules containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. Enteric coated **compositions** of the invention may be advantageous, depending on the nature of the active compound. The tablets and capsules may conveniently each contain 1-500 mg of the active medicament. Other **compositions** for oral administration include, for example, aqueous suspensions in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

SUMM **Compositions** of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example suppositories with semi-synthetic glycerides or polyethylene glycol bases.

SUMM **Compositions** of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous and oily media or sterile solutions in a suitable solvent.

SUMM **Compositions** for topical administration may comprise a matrix in which the active compound is dispersed so that it is held in contact with the skin in order to administer the medicament transdermally. Alternatively the active medicament may be dispersed in a cream or ointment base.

SUMM The nitrite and iminium ion scavengers of the present invention can also be used during the **preparation** of nitrosatable amine materials such as nitrosatable surfactants, herbicides and pharmaceuticals, for example in the manner described in European Patent Publication No. 498346 (Albright & Wilson).

SUMM Thus the present invention further provides a method of stabilising a nitrosatable amine material to inhibit the formation of nitrosamines by adding to the material an effective amount of an iminium ion scavenger and optionally a nitrate ion scavenger as defined above. The scavengers may be added either before,during or after the **preparation** of the amine material.

SUMM The effect of various iminium ion scavengers on the formation of nitrosamines in a typical bath gel-type formulation was investigated. The gel (Gel 1) had the following **composition**:

SUMM TABLE 1

N-nitrosamine (R.sub.2 NNO) inhibition in bath gel (Gel 1) with 5 mM morpholine and
5 mM diethanolamine at 22.degree. C. (**pH** 7)
Initial bronopol concentration = 1 mM

Inhibitor (concentration in % [nitrite])	[R.sub.2 NNO] [nitrite]	[R.sub.2 NNO]

			%			
brackets)						
	ppm NO					
		ppb NO				
			inhibition			
				ppm NO		
					ppb NO	
						inhibition
TIME	28 days			56 days		
trisodium citrate						
	2.3	90	46	4.9	240	17
(10 mM)						
trisodium citrate						
	4.5	120	-9	4.9	190	17
(100 mM)						
potassium fluoride						
	2.8	150	11	5.8	290	-4
(10 mM)						
potassium fluoride						
	1.3	210	-90	5.8	230	0
(100 mM)						

TIME	84 days			196 days		
trisodium citrate						
	6.4	275	43	6.9	240	70
(10 mM)						
trisodium citrate						
	6.7	310	6	7.4	140	82
(100 mM)						
potassium fluoride				6.4	260	68
(10 mM)						
potassium fluoride				7.2	230	71
(100 mM)						

SUMM TABLE 2

N-nitrosamine (R.sub.2 NNO) inhibition in bath gel (Gel 1) with 5 mM morpholine and 5 mM diethanolamine at 40.degree. C. (**pH** 7)
Initial bronopol concentration = 1 mM

Inhibitor						
(concentration in						
	[nitrite]					
		[R.sub.2 NNO]				
			%	[nitrite]		
					[R.sub.2 NNO]	
						%
brackets)	ppm NO					
		ppb NO				
			inhibition			
				ppm NO		
					ppm NO	
						inhibitior
TIME	28 days			56 days		
ammonium bicarbonate (10 mM)	12	290	60	13	560	53
ammonium bicarbonate (100 mM)	19	320	48	17	530	56
ammonium bicarbonate (10 mM)	8.8	350	52	12	400	67
ammonium bicarbonate (100 mM)	12	510	18	11	480	60

trisodium citrate
10 120 84 10 210 82
(10 mM)
trisodium citrate
8.8 150 76 10 160 86
(100 mM)
potassium fluoride
7.2 190 74 8.4 180 85
(10 mM)
potassium fluoride
7.3 180 71 10 230 81
(100 mM)
n-Pr-gallate (10 mM)
4.9 270 63 3.7 520 57
2-amino-2-methyl-
10 310 57 11 430 64
propanol (10 mM)
2-amino-2-methyl-
13 130 79 13 630 48
propanol (100 mM)
TIME 84 days 196 days
trisodium citrate
10.3 237 88 10 230 91
(10 mM)
trisodium citrate
6.4 185 91 11 210 93
(100 mM)
potassium fluoride 11 180 85
(10 mM)
potassium fluoride 12 580 82
(100 mM)

SUMM 300 mg of Gel 1 was mixed with an aliquot (600 .mu.l) of morpholine (2.5M) and diethanolamine in absolute ethanol and the resulting mixture was stirred for one hour. The mixture was then adjusted to **pH** 7 with aqueous acetic acid (1M) and/or aqueous sodium hydroxide (0.1M) and stirred for a further hour. An aliquot of aqueous bronopol (300 .mu.l; 1M) was then added and the resulting mixture stirred for a further hour. The mixture was then divided into four 60 cm.sup.3 portions and to each portion was added either:

SUMM TABLE 6

Total Nitrosamines (R.sub.2 NNO) in cream base (Cream Base 1) with trisodium citrate

Time (days)	[Trisodium Citrate] mM	Temp .degree.C.	**pH**	[Nitrite] ppm NO	[R.sub.2 NNO] ppb NO	Inhibition %
28	0	22	6.2	2.2	78	
28	10	22		2.3	82	0
28	0	40	5.9	4.0	340	
28	10	40	6.7	6.1	185	47
56	0	40	5.7	4.4	1020	
56	10	40	6.7	9.6	390	62
84	0	22	6.2	0.98	230	
84	10	22	6.7	1.5	200	13
84	0	40	5.6	3.1	1830	

84	10		40	6.2	8.0	480	76

SUMM TABLE 7

N-Nitrosamine Inhibition in bath gel (Gel 1) by disodium 3,3-dimethylglutarate (Na.sub.2 DMG)

Time (days)	Initial [Na.sub.2 DMG] mM	bronopol conc mM	Initial pH	Temp .degree.C.	[Nitrite].dagger. pH	[R.sub.2 NNO]* ppm NO	Inhibition ppb NO	%
28	0	1	6.8	40	6.0	16	1460	
28	10	1	6.8	40	5.4	4.7	300	79
28	0	1	6.8	22	6.6	6.1	130	
28	10	1	6.8	22	5.4	0.57	31	77
28	0	10	4.8	22	4.7	0.45	94	
28	10	10	4.8	22	4.8	0.60	54	42
28	0	1	4.8	22	4.8	2.5	30	
28	10	1	4.8	22	2.1	28	7	
28	0	1	4.8	40	4.8	2.7	570	
28	10	1	4.8	40	4.7	0.8	550	4
56	0	1	6.8	40	6.4	19	8390	
56	10	1	6.8	40	5.4	3.1	1670	80
56	0	1	6.8	22	6.7	8.8	380	
56	10	1	6.8	22	5.4	0.98	61	84

56	0	10	4.8					
				22	4.7			
						0.97	170	
56	10	10	4.8					
				22	4.8			
						0.87	125	26
56	0	1	4.8					
				22		0.25	43	
56	10	1	4.8					
				22		0.3	43	
56	0	1	4.8					
				40		1.6	1090	
56	10	1	4.8					
				40		0.9	760	31
84	0	1	6.8					
				40		12	6280	
84	10	1	6.8					
				40		4.6	2580	59
84	0	1	6.8					
				22		11	560	
84	10	1	6.8					
				22		0.95	85	85
84	0	10	4.8					
				22		1.6	260	
84	10	10	4.8					
				22		1.6	310	-19

.dagger.Initial nitrite concentration in range 0.30-0.49 ppm NO;
*Initial NNitrosamine concentration below 20 ppb NO

SUMM TABLE 8

N-Nitrosamine (R.sub.2 NNO) Inhibition in Bath Gel (Gel 1) by Trisodium Citrate and Ascorbic Acid at 40.degree. C. and Initial **pH** of 5

Time (days)	[ascorbic acid].sub.0 mM	**pH**	[Nitrite] ppm NO	[R.sub.2 NNO]* ppm NO	inhibition %
0	0		0.95	<0.02	
0	10		0.22	<0.02	
28	0	4.9	17	28	
28	10	5.0	0.9	11.4	59
56	0	4.9	17	75	
56	10	5	0	14	81

* = Initial nitrosamine concentration below 20 ppb NO

SUMM An aliquot (500 .mu.l) of a solution of morpholine (1M) and diethanolamine (1M) in water plus an aliquot (2 cm.sup.3) of a solution of sodium citrate (0.5M) and ascorbic acid (0.5M), adjusted to the required **pH** with aqueous acetic acid (1M) and aqueous sodium hydroxide (2M), were added sequentially to a sample (100 g) of the bath gel (Gel 1) described above. The resulting mixture was stirred for about one hour. The **pH** was further adjusted with aqueous acetic acid (1M) and aqueous sodium hydroxide (2M). Bronopol (1 cm.sup.3 ; 0.1M) was added, the resulting mixture was stirred for a further hour, then transferred to 5 cm.sup.3 amber ampoules and stored for up to 84 days at either 22.degree. C. or 40.degree. C. As a control, this procedure was repeated with the modification that water (2 cm.sup.3) was added in place of the solution of sodium citrate and ascorbic acid, after **pH** adjustment and addition of bronopol. Each mixture was analysed as described in Test A above at 28 days and 56 days and, where

possible, at 84 days, to determine both nitrite and total N-nitrosamine concentrations. The results are set out below in Table 9 (for samples stored at 22.degree. C.) and Table 10 (for samples stored at 40.degree. C.).

SUMM

TABLE 9

Nitrosamine (R.sub.2 NNO) inhibition by trisodium citrate (10 mM) and ascorbic acid (10 mM) in bath gel (Gel 1) with 5 mM morpholine and 5 mM diethanolamine at 22.degree. C.
Initial bronopol concentration = 1 mM

Time (days)	Inhibitors (concentration in brackets)	pH	[nitrite] ppm NO	[R.sub.2 NNO] ppm NO	% inhibition.sup.a
28	None (control)	7	6.5	110	
28	trisodium citrate (10 mM) + ascorbic acid (10 mM)	7	5.1	100	9
28	None (control)	6	0.6	42	
28	trisodium citrate (10 mM) + ascorbic acid (10 mM)	6	1.0	114	-171
28	None (control)	5	0.16	33	
28	trisodium citrate (10 mM) + ascorbic acid (10 mM)	5	0.14	160	-38
56	None (control)	7	9.7	270	
56	trisodium citrate (10 mM) + ascorbic acid (10 mM)	7	1.5	130	52
56	None (control)	6	1.5	51	
56	trisodium citrate (10 mM) + ascorbic acid (10 mM)	6	0.21	78	-53
56	None (control)	5	0.23	44	
56	trisodium citrate (10 mM) + ascorbic acid (10 mM)	5	0.22	69	-57
84	None (control)	7	9.0	420	
84	trisodium citrate (10 mM) + ascorbic acid (10 mM)	7	1.1	100	76
196	None (control)	7	8.3	830	
196	trissodium citrate (10 mM) + ascorbic acid (10 mM)	7	0.13	134	83
196	None (control)	6	2.3	200	

196	trisodium citrate (10 mM) + ascorbic acid (10 mM)	6	1.9	55	72
196	None (control)	5	0.5	80(.+-.20)	
196	trisodium citrate (10 mM) + ascorbic acid (10 mM)	5	0	50(.+-.25)	38

.sup.a Relative to line above

SUMM TABLE 10

Nitrosamine (R.sub.2 NNO) inhibition by trisodium citrate (10 mM) and ascorbic acid (10 mM) in bath gel (Gel 1) with 5 mM morpholine and 5 mM diethanolamine at 40.degree. C.
Initial bronopol concentration = 1 mM

Time (days)	Inhibitors (concentration in brackets)	pH	[nitrite] ppm NO	[R.sub.2 NNO] ppm NO	% inhibition.sup.a
28	None (control)	7	15	710	
28	trisodium citrate (10 mM) + ascorbic acid (10 mM)	7	0.39	97	86
28	None (control)	6	6	--	
28	trisodium citrate (10 mM) + ascorbic acid (10 mM)	6	4.5	100	--
28	None (control)	5	0.39	110	
28	trisodium citrate (10 mM) + ascorbic acid (10 mM)	5	0.04	33	70
56	None (control)	7	12.7	1330	
56	trisodium citrate (10 mM) + ascorbic acid (10 mM)	7	0.2	170	86
56	None (control)	6	1.5	930	
56	trisodium citrate (10 mM) + ascorbic acid (10 mM)	6	0.2	90	90
56	None (control)	5	2.22	290	
56	trisodium citrate	5	0	170	41

(10 mM) +
ascorbic acid (10 mM)
84 None (control)
7 11.4 1710
84 trisodium citrate
7 0.02 130 92
(10 mM) +
ascorbic acid (10 mM)
84 None (control)
6 3.6 870
84 trisodium citrate
6 0.6 140 83
(10 mM) +
ascorbic acid (10 mM)
84 None (control)
5 0.18 660
84 trisodium citrate
5 0.2 62 90
(10 mM) +
ascorbic acid (10 mM)
196 None (control)
7 12.6 4500
196 trisodium citrate
7 0.06 130 97
(10 mM) +
ascorbic acid (10 mM)
196 None (control)
6 2.7 1550
196 trisodium citrate
6 0.01 100 93
(10 mM) +
ascorbic acid (10 mM)
196 None (control)
5 0.7 1020
196 trisodium citrate
5 0.02 40 95
(10 mM) +
ascorbic acid (10 mM)

.sup.a Relative to line above
.sup.a Relative to control (see line above in table)

SUMM Reactant solutions containing morpholine (11-88 mM), formaldehyde (0-140 mM), sodium nitrite (1-4 mM) and inhibitors where relevant in 20% (v/v) ethanol: water at the required **pH** (by adjustment with perchloric acid (5M) or sodium hydroxide (2M)) and contained in sealed, amber glass ampoules (5 cm.sup.3) were placed in a thermostatted bath at 25.degree. C. At regular time intervals, ampoules were withdrawn and cooled in ice. An aliquot (1 cm.sup.3) was added to aqueous sulphamic acid (1 cm.sup.3 ; 1M) containing N-nitrosopiperidine (100 .mu.l, 0.7-1.4 mM) as internal standard and pyrrolidine (100 .mu.l, 100 mM) as an artifact control. After thorough mixing and standing for approximately 10 minutes, this solution was extracted with dichloromethane (2 cm.sup.3), dried over sodium sulphate and then assayed for nitrosamines by capillary gas chromatography (isothermally at 110.degree. C. on a BP20 (SGE, 12 m.times.0 33 mm id) silica column). Under these conditions, the retention times (with base-line separation) were N-nitrosopiperidine (2.3 minutes) N-nitrosopyrrolidine (2.8 minutes) and N-nitrosomorpholine (3.5 minutes).

SUMM The studies were carried out at **pH** 5-7 and 25.degree. C. using an approximately 10-fold excess of morpholine, low concentrations (1-4 mM) of sodium nitrite and varying amounts of formaldehyde up to 70 mM (2100 ppm). Initial rates (r.sub.o =d[N-nitrosomorpholine]/dt) of

N-nitroso-morpholine formation were obtained from data over the first 6% of reaction and converted into pseudo first-order initial rate coefficients (k.sub.o) via equation I. Results are set out in Table 12.

SUMM TABLE 12

Variation of k.sub.0 with [trisodium citrate] for the nitrosation of morpholine at **pH** 7 and 25.degree. C. [Morpholine].sub.0 = 44 mM, [formaldehyde].sub.0 = 70 mM, [sodium nitrite].sub.0 = 4 mM.

10.sup.3 [trisodium citrate] mM	10.sup.6 k.sub.o s.sup.-1
0	4.0
0.5	3.6
1	2.7
10	1.5
25	1.1
100	1.2
100.sup.a	1.9
1000	0.8

.sup.a In presence of 100 mM ascorbic acid.

SUMM Further kinetic studies were carried out by taking initial rate measurements in 80% (v/v) aqueous-ethanol acetate buffers (100 mM) at **pH** 5 and at **pH** 7 and 25.degree. C. using 44 mM morpholine and 0.8 mM sodium nitrite. Results are set out in Tables 13 and 14.

SUMM TABLE 14

Inhibition of N-nitrosomorpholine formation via the iminium ion pathway at 25.degree. C. by neutral salts: Initial **pH** = 7; [Morpholine].sub.0 = 44 mM; [formaldehyde].sub.0 = 70 mM; [sodium nitrite].sub.0 = 4 mM

Inhibitor	1 mM	10.sup.6 k.sub.0 /s.sup.-1 10 mM
None	4.0	
Trisodium citrate	2.7	1.5
Disodium 3,3-dimethylglutarate	1.1	1.6
Sodium bicarbonate	1.8	1.3
Sodium fluoride	1.1	1.2
Sodium bicarbonate	1.4	1.1
Sodium iodide	1.2	1.6
Sodium thiocyanate	2.0	1.5
Disodium adipate		1.3
Disodium succinate		1.6
Disodium maleate		1.4

SUMM TABLE 15

N-Nitrosamine inhibition in bath gel (Gel 1) at 22.degree. C.; [Morpholine].sub.0 =

5 mM; [Additive].sub.0 = 10 mM; [Disodium dimethylglutarate].sub.0 = 10 mM

Time (days)		pH	[NO.sub.2]/ ppm NO	[R.sub.2 NNO]/ppb NO	Inhib/%
	Inhibitor added				
83	None (control)				
		7	7.3	510	
83	IAA	7	0.9	110	78
83	KA	7	2.9	76	85
83	None (control)				
		6	2.5	200	
83	IAA	6	0.34	160	20
83	KA	6	0.7	87	57
83	None (control)				
		5	0.27	340	
83	IAA	5	0.12	64	81
83	KA	5	0.21	65	81
	Additive				
196	None (control)				
		7	9.1	670	
196	IAA	7	0.19	77	88
196	KA	7	2.2	130	80
196	None (control)				
		6	4.5	340	
196	IAA	6	0.07	60	82
196	KA	6			
196	None (control)				
		5	0.8	280	
196	IAA	5	0.15	70	75
196	KA	5	0.2	65	77

SUMM TABLE 16

N-Nitrosamine inhibition in bath gel (Gel 1) at 40.degree. C. [Morpholine].sub.0 = [Diethanolamine].sub.0 = 5 mM; [Additive].sub.0 = 10 mM; [Disodium dimethylglutarate].sub.0 = 10 mM

Time (days)	Additive	pH	[NO.sub.2]/ ppm NO	[R.sub.2 NNO]/ppb NO	Inhib/%
28	None (control)				
		7	12.7	900	
28	IAA	7	1.3	51	94
28	KA	7	3.1	224	75
28	None (control)				
		6	10.1	860	
28	IAA	6	1.8	41	95
28	KA	6	1.9	430	50
28	None (control)				
		5	2.5	400	
28	IAA	5	2.3	108	73
28	KA	5	0.2	126	68
54	None (control)				
		7	12.9	2700	
54	IAA	7	0.065	80	97
54	KA	7	0.85	224	92
54	None (control)				
		6	7.7	1960	
54	IAA	6	0.04	36	98

54	KA	6	0.15	410	79
54	None (control)				
		5	2.5	1050	
54	IAA	5	0.02	20	98
54	KA	5	0.02	85	92
85	None (control)				
		7	7.9	2140	
85	IAA	7	0.06	80	96
85	KA	7	0.26	240	89
85	None (control)				
		6	7.2	3170	
85	IAA	6	0	42	99
85	KA	6	0.15	270	95
85	None (control)				
		5	2.9	2085	
85	IAA	5	0	21	99
85	KA	5	0.03	85	96
196	None (control)				
		7	10.5	3370	
196	IAA	7	0.02	120	96
196	KA	7	0	270	92
196	None (control)				
		6	1.7	1950	
196	IAA	6	0.06	36	98
196	KA	6			
196	None (control)				
		5	1.8	5580	
196	IAA	5	0.03	147	97
196	KA	5	a	a	

a = ampoule broken during storage
NB Control samples do not contain DMG

SUMM TABLE 17

N-Nitrosamine inhibition in cream (Cream Base 2) at 22.degree. C.;
[Morpholine].sub.0 = [Diethanolamine].sub.0 = 5 mM;
[Additive].sub.0 = 10 mM; [disodium dimethylglutarate].sub.0 = 10 mM

Time (days)	Additive	pH	ppm NO	[R.sub.2 NNO]/ppb NO Inhib/%
84	None (control)			
		7	8.3	1250	
84	IAA	7	1.4	460	63
84	KA	7	4.7	430	66
84	None (control)				
		6	5.7	520	
84	IAA	6	0.44	220	58
84	KA	6	2.9	270	48
84	None (control)				
		5	2.5	100	
84	IAA	5	0.52	185	-85
84	KA	5	0.51	190	-90
196	None (control)				
		7	6.4	1940	
196	IAA	7	1.4	490	75
196	HMT	7			
196	KA	7	2.1	780	60
196	None (control)				
		6	3.5	1530	
196	IAA	6	0.01	68	96
196	KA	6	0.4	560	63

196	None (control)				
		5	0.6	260	
196	IAA	5	0.1	100	62
196	KA	5	0.2	83	68

SUMM TABLE 18

N-Nitrosamine inhibition in Cream Base 2 at 40.degree. C.; [Morpholine].sub.0 = [Diethanolamine].sub.0 = 5 mM; [Additive].sub.0 = 10 mM; [Disodium dimethylglutarate].sub.0 = 10 mM

Time (days)	Additive	**pH**	ppm NO [R.sub.2 NNO]/[NO.sub.2]/ppb NO		Inhib/%
21	None (control)				
		7	24	2080	
21	IAA	7	1.7	480	77
21	KA	7	1.5	440	79
21	None (control)				
		6	7.4	1850	
21	IAA	6	0.58	55	97
21	KA	6	2.2	1060	42
21	None (control)				
		5	1.0	1020	
21	IAA	5	0.2	170	83
21	KA	5	0.3	320	69
56	None (control)				
		7	7.7	4870	
56	IAA	7	0.9	590	88
56	KA	7	0.19	540	89
56	None (control)				
		6	1.5	4100	
56	IAA	6	0.01	56	99
56	KA	6	0.15	1530	63
56	None (control)				
		5	0.6	1240	
56	IAA	5	0.2	60	95
56	KA	5	0.05	200	84
88	None (control)				
		7	2.7	7340	
88	IAA	7	1.9	720	90
88	KA	7	0.07	450	94
88	None (control)				
		6	4.0	4260	
88	IAA	6	2.4	51	99
88	KA	6	3.7	200	95
88	None (control)				
		5	0.9	1630	
88	IAA	5	0	63	96
88	KA	5	a	a	
196	None (control)				
		7	2.6	6670	
196	IAA	7	0.3	1290	80
196	KA	7	a	a	
196	None (control)				
		6	1.0	2430	
196	IAA	6	0	41	98
196	KA	6	0	1750	30
196	None (control)				
		5	0.3	910	
196	IAA	5	0.01	39	96

196 KA 5 a a

a = ampoule broken during storage
NB Control samples do not contain DMG

DETD An oil-free skin gel is prepared in conventional manner to the following **composition**:

DETD A self-foaming shaving gel is prepared in conventional manner to the following **composition**:

DETD A suntan lotion is prepared in conventional manner to the following **composition**:

DETD A light duty liquid detergent is prepared in conventional manner to the following **composition**:

DETD A facial wash is prepared in conventional manner to the following **composition**:

CLM What is claimed is:

2. A method of inhibiting nitrosation reactions in a cosmetics or toiletries **composition** having water as a carrier material therein, which method comprises employing an iminium ion scavenger which is a member selected from the group consisting of alkali metal glutarates, alkali metal 3,3-dimethylglutarates, alkali metal citrates, alkali metal adipates, alkali metal succinates, and alkali metal maleates, in combination with a nitrite ion scavenger which is an ascorbyl phosphate.

3. The method of claim 2, in which the cosmetics or toiletries **composition** is in the form of a member selected from the group consisting of cream, gel and lotion.

7. The method of claim 2, in which the ascorbyl phosphate is **magnesium ascorbyl phosphate**.

8. The method of claim 2, wherein the iminium ion scavenger is present in a concentration of from about 0.1 mM to about 100 mM in the cosmetics or toiletries **composition**.

9. The method of claim 2, wherein the nitrite ion scavenger is present in a concentration of from about 0.01 mM to about 50 mM in the cosmetics or toiletries **composition**.

10. The method of claim 2, wherein the cosmetics or toiletries **composition** comprises a gem-bromonitro antimicrobial agent.

IT 50-81-7, Ascorbic acid, biological studies 52-51-7, Bronopol 59-02-9, .alpha.-Tocopherol 68-04-2, Trisodium citrate 77-92-9, Citric acid, biological studies 80-72-8, Reductic acid 89-65-6, Isoascorbic acid 109-00-2, 3-Hydroxypyridine 110-15-6, Succinic acid, biological studies 110-16-7, Maleic acid, biological studies 118-71-8, Maltol 120-80-9, Catechol, biological studies 121-79-9, n-Propyl gallate **123-31-9**, Hydroquinone, biological studies 124-04-9, Adipic acid, biological studies 124-68-5, 2-Amino-2-methylpropanol 127-09-3, Sodium acetate 128-37-0, Butylated hydroxytoluene, biological studies 144-55-8, Sodium bicarbonate, biological studies 150-90-3, Disodium succinate 371-47-1, Disodium maleate 501-30-4, Kojic acid 540-72-7, Sodium thiocyanate 765-70-8, 3-Methyl-cyclopentane-1,2-dione 994-36-5, Sodium citrate 1066-33-7, Ammonium bicarbonate 3658-77-3 4839-46-7, 3,3-Dimethylglutaric acid 4940-11-8, Ethyl maltol 7486-38-6, Disodium adipate 7558-79-4, Disodium hydrogen phosphate 7681-82-5, Sodium iodide, biological studies 7789-23-3, Potassium fluoride 13881-91-9, Aminomethylsulfonic acid 14114-09-1, 5-Methylreductic acid 25013-16-5, Butylated hydroxyanisole 29838-78-6 106579-53-7, Ascorbic acid 6-phosphate 107985-63-7, Disodium 3,3-dimethylglutarate 167973-55-9, Vitazyme C
(iminium and/or nitrite ion scavengers for cosmetics and

pharmaceuticals)

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